Original Research

CLINICAL PROFILE AND TREATMENT RESULTS OF PATIENTS RECEIVING BPALM REGIMEN FOR DRUG-RESISTANT TUBERCULOSIS AT A TERTIARY CARE TEACHING HOSPITAL: A PROSPECTIVE OBSERVATIONAL STUDY

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ABSTRACT

Background: Resistant TB is linked to long treatment duration, toxicity, poor adherence and poor outcomes. The six-month all-oral BPaLM regimen (bedaquiline, pretomanid, linezolid, moxifloxacin) is a paradigm shift in the treatment of rifampicin-resistant tuberculosis (RR-TB), however, real world data from tertiary hospitals are limited. Methods: This study characterizes clinical profile, microbiological response, safety, and treatment outcomes of BPaLM in people with drug-resistant pulmonary TB.

Methods: The study was a prospective observational study of 72 eligible patients with rifampicin resistant or multidrug resistant (MDR) pulmonary tuberculosis (PTB) started on BPaLM in a tertiary care teaching hospital. Demographic, clinical, radiological, microbiological and comorbidity data were collected as a baseline. Patients were monitored for 26 weeks of treatment and early follow-up. Sputum smear and culture conversion, weight gain, symptom improvement, treatment success, adverse events and factors associated with unfavourable outcome were the outcomes.

Results: Mean age was 36.8 +/- 12.7 years; 46 (63.9%) were male. Diabetes was present in 13 (18.1%), HIV infection in 4 (5.6%), and cavitary disease in 39 (54.2%). Culture conversion occurred in 53 (73.6%) by 8 weeks and 65 (90.3%) by 12 weeks. There was an overall success in treatment of 64/72 (88.9%) including 54 cured and 10 treatment completed. The adverse events were death (3, 4.2%), treatment failure (2, 2.8%) and loss to follow-up (3, 4.2%). Anaemia occurred in 22 (30.6%), peripheral neuropathy in 13 (18.1%), QTc prolongation above 500 ms in 3 (4.2%), and linezolid dose modification in 16 (22.2%).

Conclusions: BPaLM had high early culture conversion rate and satisfactory treatment outcomes with low toxicity in a hospital environment of tertiary teaching center.

Keywords: BPaLM, Drug-Resistant Tuberculosis, Rifampicin-Resistant Tuberculosis, MDR-TB, Bedaquiline, Pretomanid; Linezolid, Treatment Outcomes.

INTRODUCTION

Tuberculosis is still a huge problem as an infectious disease in the world and MDR TB poses a threat to the progress on tuberculosis elimination. The diagnosis and rapid confirmation of multidrug-resistant and rifampicin-resistant tuberculosis (MDR/RR-TB), effective regimens, drug susceptibility testing, and adherence support are critical. World Health Organization reported persistently low treatment coverage for MDR/RR-TB despite all-oral treatment regimens increasing the success rate in countries around the world [1].

www.ajmrhs.com
eISSN: 2583-7761

Date of Received: 15-05-2026
Date Acceptance: 25-05-2026
Date of Publication: 24-06-2026

The MDR/RR-TB treatment was 18-24 months in length, included injectable drugs, was costly and had a significant pill burden and intermittent therapy. These constraints led to sub-optimal compliance, high cost, acquired resistance and bad results. Awareness of these issues prompted the creation of shorter all-oral treatment regimens with newer and existing agents with greater sterilizing activity [2].

One of the first breakthroughs in the treatment of MDR-TB was the discovery of Bedaquiline, a diarylquinoline that acts as an inhibitor of mycobacterial ATP synthase. In clinical trials, bedaquiline did not demonstrate significant clinical effects when used as background therapy; use of bedaquiline in background therapy had positive effects on culture conversion, but QT prolongation

and resistance monitoring were noted. Later, pretomanid, a nitroimidazole, and linezolid, an oxazolidinone with potent antimycobacterial properties, were found to be important ingredients of highly active oral combinations to treat resistant tuberculosis [4, 5].

The Nix-TB trial proved that a six-month BPaL (bedaquiline/pretomanid/linezolid) treatment of highly drug-resistant TB (HDR-TB) was associated with improved clinical outcomes, while linezolid was associated with neuropathy and myelosuppression were prominent [6]. The ZeNix trial later demonstrated that linezolid dose, and duration, modification resulted in similar efficacy and decreased toxicity [7]. The results laid the foundations for the development of the BPaL backbone as a strong short-course alternative for drug-resistant tuberculosis cases.

The TB-PRACTECAL trial expanded on this evidence to assess all-oral treatment regimens for pulmonary TB that are resistant to rifampicin. The BPaLM regimen (bedaquiline, pretomanid, linezolid, and moxifloxacin) was noninferior and superior to standard care in the primary composite outcome and was better tolerated [8]. Subsequent analyses and evidence focused on implementation showed that BPaLM improves outcomes by shortening treatment duration and the number of pills and toxicity, when compared with traditional longer treatment regimens [9, 10].

Based on the WHO guidance, 6-month BPaLM/BPaL regimens are now recommended for eligible patients with MDR/RR-TB, and the choice of regimen is made based on the fluoroquinolone susceptibility, prior exposure to TB treatment, presence of extrapulmonary disease, pregnancy status, age and contraindications [11]. But the success of BPaLM in programmatic contexts requires baseline evaluation, ECG monitoring, haemoglobin surveillance, management of linezolid toxicity and adherence counselling, as well as timely microbiological follow-up. Results from teaching hospitals are therefore critical to determine real-world barriers and patients subsets that need better monitoring.

India has a substantial burden of MDR TB and is making a beginning in the programmematic scale-up of all-oral, shorter regimens. A tertiary care teaching hospital may have to deal with patients who have diabetes, a complicated radiological disease, previous drug exposure history, referrals with a delayed response and adverse drug reactions. In this prospective observational study, the authors sought to describe the clinical profile, microbiological response, the safety profile and treatment outcomes of BPaLM therapy in patients with drug-resistant pulmonary tuberculosis at a tertiary care teaching hospital.

MATERIALS AND METHODS

Over a period 18 months, a prospective observational study was conducted in the Department of Respiratory Medicine and the nodal drug resistant tuberculosis (DRTB) centre of a tertiary level teaching hospital. After obtaining written informed consent, eligible patients who started BPaLM were enrolled in the study.Eligible patients who began BPaLM were subsequently enrolled on the study. The study was non-interventional, with no changes made to the selection, monitoring or clinical management of the regimen as per the national tuberculosis programme. For estimation of treatment success, sample size was calculated. The minimum sample size required when assuming the favorable assumption is 85%, the absolute precision is 8% and a 95% confidence level is required is 61 patients. Of the 72 patients, 70 were considered for analysis (two dropped out prematurely).

Those who were eligible for BPaLM after the review of drug susceptibility were included in this group and had been diagnosed with either BDR-PTB or RR-PTB.The patients included were aged 14 years and older and had been bacteriological confirmed with BDR-PTB or RR-PTB and eligible for BPaLM. No contraindications to bedaquiline, pretomanid, linezolid or moxifloxacin were known, QTc < 500 ms, and attendance at follow-up. Exclusion criteria were pregnancy or lactation, severe baseline peripheral neuropathy, severe anaemia (haemoglobin <8 g/dL), severe hepatic dysfunction, extrapulmonary tuberculosis without pulmonary involvement, and documented resistance or intolerance which required a non-BPaLM regimen, refusal of consent.

Baseline assessment comprised of age, sex, body mass index, smoking and alcohol history, history of previous treatment for TB, comorbidities, HIV status, diabetes status, symptoms, sputum smear grade, Xpert MTB/RIF, or line probe assay result, culture and phenotypic or molecular drug-susceptibility testing where available, chest radiograph findings, complete blood count, liver and renal function tests, electrolytes, random blood sugar, ECG, and audiovestibular and neurological evaluation when indicated.

The BPaLM regimen comprised of bedaquiline, pretomanid, linezolid, and moxifloxacin for a period of 26 weeks as recommended by the program. Bedaquiline was given in a loading phase followed by continuation dosing thrice weekly; Pretomanid was given at programme-recommended dose, modified for toxicity; Linezolid was started at programme-recommended dose and adjusted for toxicity. Pyridoxine, nutritional counselling, adherence support and adverse-event counselling were provided. The decision to modify doses, temporarily withhold treatment, and to provide

supportive therapy was determined by the treating specialist and programme committee. Patients were seen at baseline, 2 weeks, monthly during treatment, end of treatment and early post-treatment visit. Sputum smear and culture were done at the baseline and at regular follow-up. Symptom improvement, resolution of fever, reduction in the number of coughs, appetite, weight gain, and functional status were the measures used to assess clinical response. Safety monitoring consisted of haemoglobin, platelet counts, liver enzymes, neuropathy symptoms, visual complaints, gastrointestinal intolerance, and serial ECG and QTc calculation. The outcomes of treatment were classified as cured, completed treatment, treatment failure, death, loss to follow up and not evaluated according to programme definitions. Cured/Completed treatment was considered to be a cured case. The primary outcome was treatment success at end of treatment (EOT). Secondary outcomes included: culture conversion at 8-weeks; culture conversion at 12-weeks; adverse events; serious adverse events; linezolid dose modification; QTc prolongation; and factors associated with unfavourable outcome.

The SPSS version 26 was used for analysing the data. All continuous variables were presented as mean/standard deviation or median/Interquartile range and categorical variables were presented as frequency and percentage. Independent t-test, Mann-Whitney U test, chi-square test, or Fisher exact test was used to compare groups of favourable versus unfavourable outcomes. The variables with $p<0.10$ in univariate analysis were explored in logistic regression, because the number of unfavourable outcomes was small. The p-value of < 0.05 was regarded as a statistical significance.

RESULTS

A total of 72 patients receiving BPaLM were included. The cohort was predominantly young to middle-aged, male, and previously treated for tuberculosis. More than half had cavitary disease, and nearly one-fifth had diabetes mellitus. Baseline characteristics are summarized in Table 1.

Table 1: Baseline Clinical Profile of Patients Receiving BPaLM

Variable	Value (N=72)
Age (years), mean +/- SD	36.8 +/- 12.7
Male sex, n (%)	46 (63.9)
BMI (kg/m2), mean +/- SD	18.7 +/- 3.1
Previous anti-TB treatment, n (%)	49 (68.1)
Current smoker, n (%)	21 (29.2)
Diabetes mellitus, n (%)	13 (18.1)
HIV infection, n (%)	4 (5.6)
Cavitary disease on chest radiograph, n (%)	39 (54.2)
Bilateral lung involvement, n (%)	34 (47.2)
Baseline smear positive, n (%)	58 (80.6)
RR-TB, n (%)	31 (43.1)
MDR-TB, n (%)	41 (56.9)

The most common symptoms were cough (91.7%), weight loss (76.4%), fever (54.2%), and dyspnoea (31.9%). Mean baseline haemoglobin was 11.2 +/- 1.6 g/dL, and mean QTc was 421 +/- 24 ms.

Table 2: Microbiological, Clinical, and Final Treatment Outcomes

Outcome	Value (N=72)
Sputum smear conversion by 8 weeks, n (%)	55 (76.4)
Culture conversion by 8 weeks, n (%)	53 (73.6)
Culture conversion by 12 weeks, n (%)	65 (90.3)
Mean weight gain at end of treatment (kg)	4.8 +/- 2.9
Symptom improvement by 8 weeks, n (%)	61 (84.7)
Completed 26-week regimen, n (%)	66 (91.7)
Cured, n (%)	54 (75.0)
Treatment completed, n (%)	10 (13.9)
Treatment success, n (%)	64 (88.9)
Treatment failure, n (%)	2 (2.8)
Death, n (%)	3 (4.2)
Loss to follow-up, n (%)	3 (4.2)

The majority of patients achieved early microbiological response. Treatment success was 88.9%, with death, failure, and loss to follow-up accounting for the eight unfavourable outcomes.

Table 3: Adverse Events and Factors Associated with Unfavourable Outcome

Variable	Favourable (n=64)	Unfavourable (n=8)	p-value
Any adverse event, n (%)	39 (60.9)	7 (87.5)	0.140
Anaemia, n (%)	18 (28.1)	4 (50.0)	0.220
Peripheral neuropathy, n (%)	10 (15.6)	3 (37.5)	0.129
QTc >500 ms, n (%)	2 (3.1)	1 (12.5)	0.246
Linezolid dose modification, n (%)	12 (18.8)	4 (50.0)	0.049
Diabetes mellitus, n (%)	9 (14.1)	4 (50.0)	0.016
Cavitary disease, n (%)	32 (50.0)	7 (87.5)	0.047
Baseline smear grade 2+/3+, n (%)	34 (53.1)	7 (87.5)	0.072
Culture conversion by 8 weeks, n (%)	51 (79.7)	2 (25.0)	0.001

Adverse events were common but generally manageable. Diabetes, cavitary disease, linezolid dose modification, and lack of 8-week culture conversion were significantly associated with unfavourable outcome in univariate analysis.

DISCUSSION

The present prospective observational study revealed that high treatment success with BPaLM and rapid microbiological conversion were achieved in DR-PMTB patients managed at a tertiary care teaching hospital. 12 weeks or more achieved culture conversion of more than 90% of patients and treatment success 88.9%. The results are clinically significant due to the inclusion of patients who were previously treated for tuberculosis, had low BMI, diabetes, cavitary disease, and high baseline smear positivity.

These findings are consistent with the dramatic change in the approach to treating MDR TB towards shorter all-oral treatment, taking place recently. The six-month all-oral BPaLM/BPaL regimens are being more widely used globally and are being recommended for eligible MDR/RR-TB patients by WHO [1, 11]. The treatment success achieved in this study is superior to historical performance of longer MDR/RR-TB treatment regimens, illustrating the advantage of using active drugs, short treatment, fewer pills and adherence support structures.

Our favourable outcome rate is similar to the pivotal TB-PRACTECAL trial where the all-oral four drug regimen of bedaquiline, pretomanid, linezolid and moxifloxacin was found to be more effective and safer than standard care [8]. This was confirmed by a later report in the Lancet Respiratory Medicine, which showed that short oral regimens for rifampicin-resistant tuberculosis were safe and effective [9]. The present study demonstrates the feasibility and effectiveness of trial benefits in the context of tertiary programmes when active monitoring and multidisciplinary support is provided.

The high early culture conversion rate is a key finding. Culture conversion by 8 weeks is highly correlated with ultimate favourable outcome, which makes it a good early indicator of programme. Rapid reduction in bacillary burden may be due to the combination of the bactericidal and sterilizing activity of the BPaL backbone, along with the addition of the fluoroquinolone moxifloxacin in cases of fluoroquinolone-susceptible disease. But, cavitary disease and high smear grade continued to produce a higher risk, likely due to high organism burden and poor penetration of drugs into cavities.

Toxicity was still a problem but it was not so serious. The most common adverse events were anaemia, peripheral neuropathy and gastrointestinal events. Twenty-two percent (22.2%) of patients needed to have their dose of linezolid modified and had unfavourable outcomes, which could be due to the severity of toxicity or to underlying frailty. Linezolid dose and duration has been seen to be associated with events of toxicity in ZeNix trial maintaining activity, which further is supported by active haemoglobin and neuropathy monitoring [7].

QTc prolongation >500 ms was rare, but ECG monitoring should be performed because both bedaquiline and moxifloxacin may impact cardiac repolarization. Previous bedaquiline trials have shown the need for caution, while more recent programme evidence has shown the benefits of bedaquiline-containing regimens when it comes to lowering the death toll and enhancing outcomes [3, 12, 13]. In our study, electrolyte correction, reviewing interacting drugs, and temporarily stopping if necessary were used to treat changes in the QTc interval.

Unfavourable outcome was significantly correlated with diabetes. Diabetes negatively affects immune function and enhances bacillary load, delays sputum conversion, and makes nutrition recovery difficult. This discovery could be applicable to India, where diabetes and TB are often seen together. If you have diabetes and are taking BPaLM, you might need to have more intensive glycaemic control, nutritional supplementation, early culture follow-up and improved adherence support. HIV prevalence was low in this cohort and HIV-related outcomes could not be analyzed.

Another critical factor is resistance surveillance. Reliable drug-susceptibility testing and pharmacovigilance is needed for the widespread use of bedaquiline, pretomanid and linezolid. In trials using pretomanid, Timm et al. reported no resistance to pretomanid and frequent resistance to bedaquiline in highly resistant disease or previous treatment history [14]. Baseline DST, adherence support and early investigation of non-conversion are also reinforced by studies of resistance to bedaquiline and acquired resistance during therapy [15, 16].

There are some limitations to this study. It was observational, single centre and had a limited sample size and few adverse events, which limited multivariable modelling. There was limited follow-up following initial treatment review, making the evaluation of relapse difficult. Real world programme constraints meant that drug-susceptibility testing was not available for all patients for newer drugs. However, potential data collection, serial microbiology, structured adverse-event monitoring and the representation of comorbid patients enhance the relevancy of the findings in practice.

The results suggest that BPaLM can be implemented if patients are carefully selected and safety monitoring is actively done in tertiary teaching hospitals. Intensified follow-up should be provided for high-risk patients who have diabetes, have a lot of cavitary disease, have not yet been cultured, or have had linezolid toxicity. Multicentre studies are needed in the future to assess the notions of relapse-free cure, quality of life, cost, emergence of resistance and barriers to implementation in an actual public health practice.

CONCLUSION

The BPaLM regimen resulted in a rapid culture conversion and treatment success in patients with MDR/RR pulmonary TB in this prospective tertiary hospital cohort. Active monitoring was often necessary to manage toxicity, which was often seen, and linezolid dose adjustment was frequent. Patients were identified for closer follow-up based on diabetes, cavitary disease, and lack of 8 week culture conversion. BPaLM is an excellent all-oral treatment programme with microbiological monitoring, ECG surveillance, toxicity management and adherence counselling.

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How to cite this article: Meman Mohammad Yamin Salimbhai, Dr. Alvinabanu Asifikbal Mansuri, Urvibahen Vishrambhai Ghantiya, CLINICAL PROFILE AND TREATMENT RESULTS OF PATIENTS RECEIVING BPALM REGIMEN FOR DRUG-RESISTANT TUBERCULOSIS AT A TERTIARY CARE TEACHING HOSPITAL: A PROSPECTIVE OBSERVATIONAL STUDY, Asian J. Med. Res. Health Sci., 2026; 4 (2):1084-1089.
Source of Support: Nil, Conflicts of Interest: None declared.