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Long term outcomes in drug resistant tuberculosis with Bedaquiline, Pretomanid and varying doses of Linezolid

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SUMMARY

Objectives: Assess the effectiveness of bedaquiline, pretomanid and linezolid (BPaL) regimens with varying doses and duration of linezolid at the end of 48 weeks post treatment among drug resistant tuberculosis (DR TB) patients.

Methods: Multicentric pragmatic randomized clinical trial in which BPaL regimens were given for 26 weeks for pulmonary pre extensively drug resistant tuberculosis (PreXDR TB); bedaquiline, pretomanid and linezolid 600 mg for 26 weeks (arm1), structured dose reduction arms with linezolid dose reduction from 600 to 300 mg after nine weeks (arm2) and 13 weeks (arm3). Participants were followed up for recurrence-free cure up to 48 weeks post-treatment. Whole genome sequencing in sputum samples at baseline and recurrence differentiated relapse and reinfection.

Results: Of 403 enrolled, 378 were included for the modified intent-to-treat analysis based on baseline sputum culture positivity and sensitivity to medications in the study regimen. Among them, 331(88%) had recurrence-free cure at the end of 48 weeks of post-treatment follow-up; arm1:112(87%), arm2:110(88%), arm3:109(88%). Overall, 14 (12 bacteriological and 2 clinical) recurrences (arm1-four, 2-six and 3-four) occurred; 11 recurrences occurred within 24 weeks after treatment completion; four out of 11 within the

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first 12 weeks. Of the 10 paired sputum samples available at baseline and recurrence for comparison of lineages, there were two reinfections and eight relapses.
Conclusion: Structured dose reduction arms had comparable recurrence free cure rates as linezolid 600 mg arm when given along with bedaquiline and pretomanid for 26 weeks in PreXDR TB. Most of the recurrences occurred within the first six months.

Introduction

Drug-resistant tuberculosis (DR-TB) continues to remain as an imminent risk to public health, and a common cause of mortality due to an infectious illness. Globally, the estimated number of people who developed multidrug-resistant or rifampicin-resistant tuberculosis (MDR/RR-TB) was 400,000 in 2023. Of the estimated persons who had MDR/RR-TB in 2023, it was observed that four main nations accounted for more than half of the total: India (27%), Russian Federation (7·5%), Indonesia (7·4%) and China (7·4). Nevertheless, despite this burden, globally the treatment success rates have risen to 68% with the successful implementation of bedaquiline based newer regimens for MDR/RR TB in many countries.[1]

The efficacy of a regimen is determined not only by the treatment success at the end of treatment but also by the prevention of recurrence of the disease after treatment. Recurrence after completion of TB treatment could be relapse because of the endogenous reactivation with the same *Mycobacterium tuberculosis* (*M.tb)* strain from the reservoirs of dormant bacilli or exogenous reinfection with a new strain.[2] High relapse rates are suggestive of inadequate TB treatment, whereas reinfection points towards ongoing community transmission.[2] Genotyping methods that detect variations in repetitive sequences in *M.tb* complex strains help to differentiate relapse from reinfection.[3]

Newer drugs and regimens have emerged as a pathway for successfully treating DR-TB. Combinations of bedaquiline (BDQ) and linezolid (LZD) with pretomanid (Pa) or delamanid (Dlm), as demonstrated by various studies, have shown high treatment success rates.[4–7] These combinations of all oral, non-injectable regimens also have other benefits such as increased patient compliance, shorter duration of treatment, and lower toxicities as compared to other conventional longer regimens with injectables. Despite many benefits, there are limited evidences for the long-term effectiveness of these oral shorter regimens in preventing the recurrence among DR TB patients. Recurrence rate among MDR/RRTB patients on bedaquiline-based shorter regimens containing levofloxacin or moxifloxacin, clofazimine, ethambutol, and pyrazinamide was less than one percent in a South African cohort.[8] Mortality during post-treatment follow-up was around 7%.[8] Comorbidities including HIV, poor nutritional status, extra pulmonary TB were some of the predictors for poor treatment outcomes in a cohort of patients with MDR/RRTB in Ethiopia.[9] In this era of oral shorter regimens with fewer drugs, the need to identify factors that could predict those who may have suboptimal treatment response with shorter regimen and may require a longer duration of treatment is of foremost importance. The mitochondrial toxicities of Linezolid 600 mg leading to dose modifications including treatment interruptions, dose reductions or discontinuation have been documented in earlier studies.[6,7] A simulation model by Imperial et al. predicted that Linezolid dose reduction might reduce the occurrence of associated toxicities and suggested further studies for efficacy.[10] We describe here the long-term outcomes at the end of 48 weeks of post-treatment follow-up in a cohort of DR TB patients managed with bedaquiline, pretomanid and linezolid-based regimens in which varying doses of linezolid were given for different durations.

Methods

We enrolled adults aged between 18 and 65 years of age diagnosed with pre extensively drug resistant (PreXDR) pulmonary TB i.e. *M. tb* resistant to rifampicin with or without isoniazid resistance and with additional resistance to fluoroquinolones or MDR TB with treatment intolerance or non-responsive to treatment (MDR TB $_{TI/NR}$), in a multicentric pragmatic clinical trial (ClinicalTrials.gov ID: NCT05040126, CTRI/2021/03/032189) in India. The participants were managed with bedaquiline (400 mg daily for two weeks followed by 200 mg thrice weekly), pretomanid 200 mg and linezolid dose based regimens (arm 1: linezolid 600 mg for 26 weeks; arm 2: 9 weeks of linezolid 600 mg and 17 weeks of 300 mg; arm 3: 13 weeks of linezolid 600 mg and 13 weeks of linezolid 600 mg) for a period of 26 weeks. The treatment was extended to 39 weeks based on 16th week sputum culture positivity. The primary outcome was defined as TB recurrence-free cure at the end of 48 weeks of post-treatment follow-up. We followed up those patients who were declared cured at the end of treatment (without any evidence of failure and with at least two negative consecutive sputum cultures on different occasions taken at least seven days apart at the end of treatment) for a duration of 48 weeks after treatment completion. Recurrence was defined as the occurrence of two consecutive positive cultures during post-treatment follow-up or clinical signs and symptoms with radiographic deterioration after cure at the end of treatment. The detailed study methodology had been given elsewhere.[11] The end of treatment results including effectiveness and safety are described elsewhere.[12] Post-treatment, we evaluated all participants clinically once a month for the first three months, thereafter once every three months for safety and any recurrence of TB disease. We did a clinical assessment for TB symptoms and signs, and collected two sputum specimens for acid-fast bacilli (AFB) smear and liquid culture using Mycobacterium Growth Inhibitor Tube (MGIT) assay during those quarterly visits. Any *M. tb* growth in sputum culture was tested for drug susceptibility (DST) by MGIT. We compared the drug susceptibility profiles of positive cultures at the time of recurrence with baseline DST profile to rule out the emergence of acquired drug resistance. We did Whole Genome Sequencing (WGS) in the sputum samples both at the time of enrollment and recurrence. We compared the lineages of *M.tb* complex at baseline and at the time of recurrence to differentiate relapse (endogenous reactivation) from reinfection (exogenous reinfection). Different lineages at both those time points indicate reinfection and the same lineage with the same or different resistance patterns indicate relapse or reactivation of the earlier infection. Participants had chest x-rays at two time points during post-treatment follow-up, i.e., at the end of 6 and 12 months after treatment completion. We compared the chest X-rays taken during the post-treatment follow-up with the end-of-treatment X-rays for any improvement or deterioration based on the involvement of lung zones, laterality and presence of new or existing cavities/lesions.

Phenotypic drug susceptibility testing (DST)

DST for 10 drugs was performed on MGIT for bedaquiline (1.0μg/ml), capreomycin (2·5μg/ml), clofazimine (1·0μg/ml), delamanid (0·06μg/ml), ethionamide (5·0μg/ml), kanamycin (2·5μg/ml), levofloxacin (1·0μg/ml), moxifloxacin (0·25 and 1·0μg/ml), para-aminosalicylic acid (PAS) (4·0μg/ml), pretomanid (0·5 and 2·0 μg/ml), and pyrazinamide (100 μg/ml).[13]

Whole-genome sequencing

Genomic DNA was extracted from clinical isolates using the CTAB (cetyltrimethylammonium bromide) method and purified. Purified DNA was assessed for quality and quantity using Nano DropTM and QubitTM dsDNA assay kit method (ThermoFisher Scientific, Waltham, MA, USA). Sequencing libraries were prepared using the NEBNext Ultra DNA Library preparation kit.

Genomic analyses

FastQ files generated was analyzed to get variants using samtools v1·3·1. Lineages were predicted using both SNP-based variants and region of difference (RD) analysis using the tool RD-analyzer. Repeat phenotypic testing or sequencing was not performed in the event of discrepancies as there were none for study medications.

Statistical analysis

All patients who had a favorable outcome at the end of treatment (cured) were followed up for 48 weeks post-treatment. The modified intent-to-treat (mITT) population excluded patients with resistance to any of the study drugs (bedaquiline, pretomanid, linezolid) or sputum MGIT culture negativity at baseline. The per-protocol analysis excluded participants who had consumed less than 80% of the study regimen.[12] The frequencies and proportions with 95% confidence intervals were calculated for favorable and unfavorable outcomes at the end of 48 weeks post-treatment follow-up. We used a Cox regression model to determine the predictors of unfavorable treatment outcomes, including treatment failure, recurrences, death and lost to follow-up. The predictors included baseline characteristics such as gender, age, body mass index (BMI), extent of the TB disease based on chest X ray and treatment response indicators such as sputum culture conversion at the end of 9 weeks of treatment and weight gain during treatment.

Results

Of the 403 participants enrolled in this trial, 378 were included for mITT analysis. Out of the 378 participants, 352 (93%) had a favorable outcome at the end of treatment.[12] The consort of trial participants is given in Fig. 1. At the end of 48 weeks post-treatment follow-up, 88% (331) had a recurrence-free cure (Table 1). The recurrence-free cure rates were similar across the treatment arms (arm 1 −87%, arm 2 – 88% and arm 3 - 88%. The structured dose reduction arms 2 and 3 were noninferior to arm 1 with a margin of –0·1 for recurrence-free cure. One patient died and six patients were lost to follow-up during the post-treatment follow-up in spite of all attempts to retain them in the study. There were 14/378 recurrences (four - arm 1, six - arm 2, four– arm 3) during the 48 weeks post-treatment follow-up (Table 1).

Bacteriological reversion of negative sputum culture to positive was noted in 12 patients with clinical and/or radiological deterioration, and two patients had clinical and radiological deterioration without reversion to sputum smear/culture positivity. Out of 14 patients with recurrence, lineage 2 was the commonest (nine), followed by lineage 3 (three) and lineage 4 (two) as identified by WGS at baseline. Nine patients out of 14 were from the study sites in the western part of India. Among them, lineage 2 was observed in six, lineage 3 in two and lineage 4 in one patient. There were 10 paired

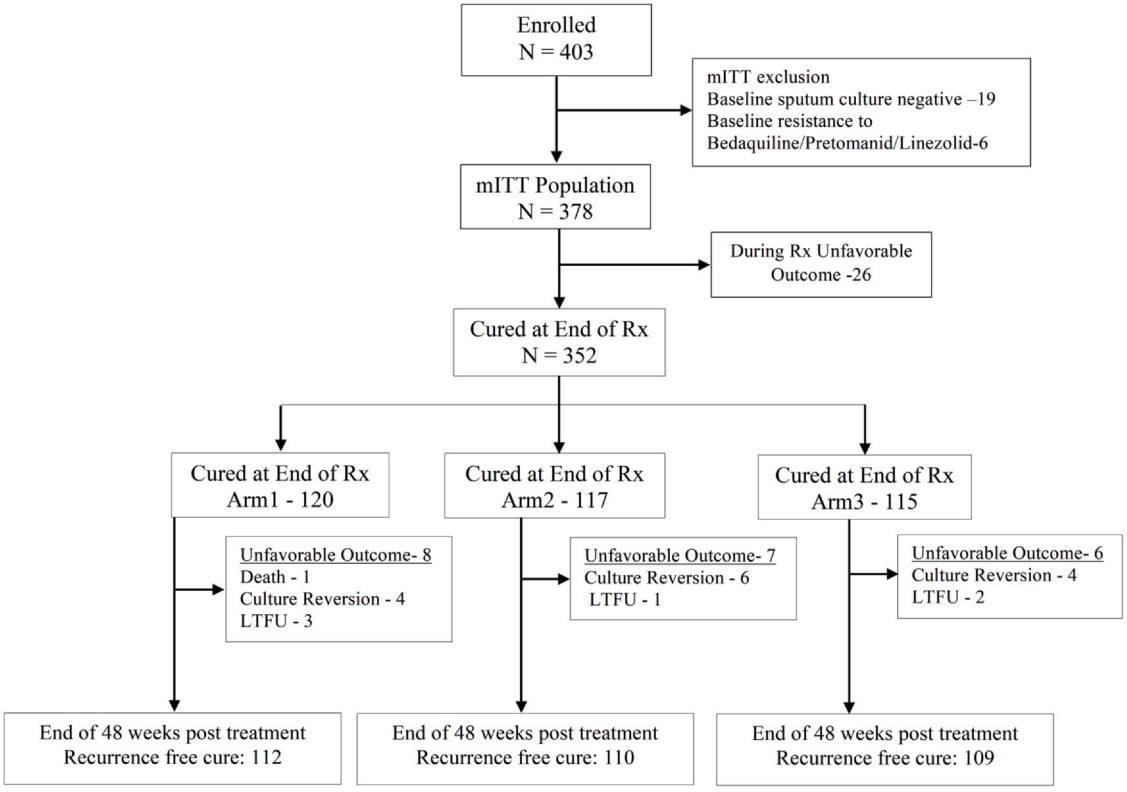

Fig. 1. Consort of mBPaL study participants.

Table 1
Effectiveness analysis (Per protocol and mITT) at the end of 48 weeks of post-treatment follow-up.

Characteristics	Arm 1 (N=135)	Arm 2 (N=135)	Arm 3 (N=133)	Total N=403
Per protocol analysis				
Assessable Population[a]	125	130	124	379
Recurrence-free cure	114 (91)	116 (89)	115 (93)	345 (91)
95% CI	85–95	82–94	87–97	88–94
Unfavorable Outcome n(%)	11 (9)	14 (11)	9 (7)	34 (9)
Treatment failure	2	5	3	10
TB recurrence	5	7	4	16
Death	1	1	0	2
Loss to follow-up	3	1	2	6
Modified Intent to Treat Analysis				
Assessable Population[b]	129	125	124	378
Recurrence free cure n(%)	112 (87)	110 (88)	109 (88)	331 (88)
95% CI	80–92	81–93	81–93	84–91
Unfavorable Outcome n(%)	17 (13)	15 (12)	15 (12)	47 (12)
Treatment failure	8	5	6	19
TB recurrence	4	6	4	14
Loss to Follow up[c]	4	1	2	7
Death[d]	1	3	3	7

[a] Those who had taken less than 80% of study medications were excluded.
[b] baseline sputum MGIT culture negative −19, Drug resistance to study medications at baseline −6 were excluded.
[c] lost to follow up during treatment −1 (arm 1).
[d] 6 deaths occurred during treatment (arm 1- 0, arm 2 −3. arm 3–3).

sputum samples available at baseline and the time of recurrence for comparison. Recurrence was due to exogenous reinfection in two patients; Lineage 4 at baseline and 3 at recurrence in one patient, lineage 2 at baseline and 3 at recurrence was observed in another patient. Both the patients with reinfection were from one study site in the northern part of India and the lineage at the time of recurrence was 3. The rest of the eight patients had endogenous reactivation (relapse) as shown by similar lineages at baseline and at the time of recurrence (Table 2).

Among 14 patients with recurrence, chest X-ray showed bilateral lung involvement in eight and cavitary lesions in six patients at the baseline. At the end of treatment, there was not much improvement in the chest X-rays of seven participants, even though there was sputum culture conversion to negative status during treatment. Regarding weight gain at the end of treatment, nine had a weight gain of 5 kg or less, four had more than 5 kg weight gain and one had lost 0·5 kg weight. Eleven of the fourteen recurrences occurred within the first 24 weeks after completion of 26 weeks of treatment, with four of them occurring within the first 12 weeks of follow-up, while two occurred at the 48th week of post-treatment follow-up. One of the patients with recurrence had treatment extended up to 39 weeks in view of the sputum culture positivity at the 16th week of treatment as per the protocol. All the patients with recurrences were started on appropriate treatment by the National TB Programme.

Table 2
Comparison of drug resistance pattern (genotypic) among mBPaL study participants at the time of recurrence (relapse and reinfection).

S.No.	Time	Arm	Amigly	Amk	Cap	Cip	Emb	ETH	FQ	Mox	Ofx	Kan	PZA	Rif	Lineage
Reinfection															
1.	Baseline	1													4
	Recurrence														3
2.	Baseline	2													2
	Recurrence														3
Relapse															
3.	Baseline	3													2
	Recurrence														2
4.	Baseline	2													2
	Recurrence														2
5.	Baseline	2													4
	Recurrence														4
6.	Baseline	3													3
	Recurrence														3
7.	Baseline	3													2
	Recurrence														2
8.	Baseline	2													3
	Recurrence														3
9.	Baseline	1													3
	Recurrence														3
10.	Baseline	2													2
	Recurrence														2

Sensitive **Resistant**

Amigly: Aminoglycosides; Amk: Amikacin; Cap: Capreomycin; Cip: Ciprofloxacin; Emb: Ethambutol; ETH: Ethionamide; FQ: Fluoroquinolone; Mox: Moxifloxacin; Ofx: Ofloxacin; Kan: Kanamycin; PZA: Pyrazinamide; Rif: Rifampicin.

Regarding the status of the Linezolid-related adverse events, out of 183 patients who had developed anemia of any grade during treatment, it resolved in 168 patients at the end of treatment. Of the 15 patients with anemia unresolved at the end of treatment, the status of anemia in 7/183 was unknown as they had unfavorable outcomes (death or treatment failure and no longer part of the trial). Eight out of 168 persons (arm 1- 4, arm 2- 1, arm 3 – 2) on follow up had unresolved anemia at the end of treatment, and among them it was unresolved in two persons [Arm 1- 1 (grade 1), arm 3 −1 (grade 2)] at the end of 48 weeks of post treatment follow up. Of the 64 patients who had thrombocytopenia during treatment, it was resolved in 55 at the end of treatment. The status was unknown/unresolved for two, as they were no longer in the follow-up due to unfavorable outcomes. One out of seven (arm 1–2, arm 2 −2, arm 3–3) with ongoing thrombocytopenia at the end of treatment had it still unresolved [arm 3 (grade 1)] at the end of post-treatment follow-up. A total of 61/66 persons with peripheral neuropathy during treatment recovered, and the status was unknown for two due to unfavorable outcomes. All three persons (arm 1–1, arm 3–2) with unresolved peripheral neuropathy at the end of treatment and who continued to be on follow-up experienced it till the end of post-treatment follow-up as well. [arm1 −1 (grade 3), arm 3 −2 (grade 1)].

Drug resistance pattern among patients with TB recurrence

Genotypic resistance testing

Resistance patterns to ethambutol, pyrazinamide, ethionamide, kanamycin, capreomycin, amikacin were noted in 14, 11, 6, 5, 4, and 1, respectively, in the culture-positive isolates of these patients (14) at baseline. Out of 12 with bacteriological recurrence during post-treatment follow-up, paired samples at baseline and recurrence were available only for 10 patients due to failure in *M.tb* growth in one sample and sequencing did not generate enough sample for analysis in another sample. The various drug resistance patterns assessed by the genotypic method (WGS) are given in Table 2. Among the injectables, acquired resistance to amikacin was observed in two patients with reinfection. Almost all had resistance to ethambutol at baseline and at the time of recurrence except for two who did not have ethambutol resistance at the time of recurrence. Resistance to pyrazinamide was noted in eight patients at baseline, among them six had at the time of recurrence as well. All had resistance to moxifloxacin and ofloxacin.

Phenotypic resistance testing (MGIT DST)

Out of 14 patients with recurrence, baseline MGIT DST results were available for all and at the time of recurrence it was available for 11 out of 12 patients with bacteriological recurrence. At baseline, resistance was observed to ethionamide in 12, pyrazinamide in eight, kanamycin in two and paraaminosalicylic acid (PAS) in two. The various resistance patterns observed for 14 drugs (Bedaquiline, Pretomanid (0.5 µg/ml and 2 µg/ml), delamanid, capreomycin, clofazimine, ethionamide, kanamycin, levofloxacin, linezolid, moxifloxacin (0.25 µg/ml and 1.0 µg/ml), PAS and pyrazinamide) by phenotypic method (MGIT DST) at baseline and at the time of recurrence are presented in Table 3. All the 11 *M. tb culture* isolates were sensitive to the study medications (bedaquiline, pretomanid, linezolid), clofazimine, and delamanid at baseline and at recurrence (Table 3).

Table 3
Comparison of drug resistance pattern (phenotypic- MGIT DST) among mBPaL study participants at the time of recurrence.

S. No.	Time Point	Arm	BD 1.0 µg/ml	CP 2.5 µg/ml	CZ 1.0 µg/ml	DM 0.06 µg/ml	ETH 5.0 µg/ml	K 2.5 µg/ml	LEVO 1.0 µg/ml	LIN 1.0 µg/ml	MOXI 0.25 µg/ml	MOXI 1.0 µg/ml	PAS 4.0 µg/ml	PTM 0.5 µg/ml	PTM 2.0 µg/ml	PZA 100 µg/ml
1.	Baseline	1	S	S	S	S	R	S	R	S	R	R	S	S	S	S
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	R
2.	Baseline	2	S	S	S	S	R	S	R	S	R	R	R	S	S	R
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	R
3.	Baseline	1	S	R	S	S	R	R	R	S	R	R	R	S	S	R
	Recurrence		S	S	S	S	R	R	R	S	R	R	S	S	S	R
4.	Baseline	3	S	S	S	S	R	S	R	S	R	R	S	S	S	R
	Recurrence		S	S	S	S	R	S	R	S	R	R	S	S	S	S
5.	Baseline	2	S	S	S	S	R	S	R	S	R	R	S	S	S	S
	Recurrence		S	S	S	S	R	S	R	S	R	R	S	S	S	R
6.	Baseline	2	S	S	S	S	S	S	R	S	R	S	S	S	S	R
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	R
7.	Baseline	3	S	S	S	S	R	S	R	S	R	S	S	S	S	R
	Recurrence		S	S	S	S	S	S	R	S	R	S	S	S	S	R
8.	Baseline	3	S	S	S	S	R	S	R	S	R	R	S	S	S	R
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	S
9.	Baseline	3	S	S	S	S	R	R	S	S	R	S	S	S	S	S
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	S
10.	Baseline	2	S	S	S	S	R	S	R	S	R	S	S	S	S	R
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	R
11.	Baseline	2	S	S	S	S	R	S	R	S	R	R	S	S	S	S
	Recurrence		S	S	S	S	R	S	R	S	R	S	S	S	S	S

Sensitive | Resistant

BD : Bedaquiline; CP: Capreomycin; CZ: Clofazamine; DM: Delamanid; ETH: Ethionamide; K: Kanamycin; Levo: Levofloxacin; LIN: Linezolid; MOXI: Moxifloxacin; PAS: Para aminosalicylic acid; PTM: Pretomanid; PZA:Pyrazinamide

Phenotype-genotype comparison

Phenotypic drug susceptibility based on genotypic predictions for all 10 paired isolates was compared with phenotypic drug susceptibility testing results for 10 antituberculous drugs. Concordance for each anti-TB drug ranged from 81.5 to 100% for first-line and second-line drugs, except for newer drugs for which the mutations are still to be cataloged.

Predictors of unfavorable treatment outcome

The predictors of unfavorable treatment outcomes including baseline characteristics, indicators of treatment response are presented in Table 4. From the baseline characteristics, previous history of treatment was significant during unadjusted analysis, however, it was not so in multivariable analysis. Regarding the treatment response indicators, sputum culture conversion on or before nine weeks of treatment (HR=0·42 (0·2 – 0·87; p value = 0·02) and weight gain of more than five kg. during treatment (HR= 0·31 (0·13 – 0·74); p = 0·01) were indicative of a favorable treatment response in multivariable analysis.

Discussion

Recurrence-free cure at the end of 48 weeks of post-treatment follow-up in our cohort of patients who were predominantly diagnosed with PreXDR TB was 88% and similar across the three treatment arms. The structured linezolid dose reduction arms were noninferior to linezolid 600 mg arm in effectiveness at the end of 48 weeks of post-treatment follow-up. The treatment success at the end of treatment among PreXDR /MDR TB patients managed with bedaquiline, pretomanid, linezolid (BPaL) and moxifloxacin (BPaLM) regimens was 82·1% in Thailand. However, this was reported from a smaller cohort of 28 patients.[14] Other trials which had studied bedaquiline, pretomanid and linezolid 600 mg for 26 weeks such as ZeNiX trial showed a favorable outcome of 89% at the end of 78 weeks of post treatment follow up.[6] BPaL arm in the TB PRACTECAL trial showed an unfavorable outcome (composite outcome) of 23% at the end of 72 weeks post-randomization.[5] EndTB-Q trial showed a favorable outcome of 85.8% at 39 weeks post-randomization with bedaquiline, delamanid, clofazimine, and linezolid (BDCL) regimen in preXDR TB patients.[15]

Most of the recurrences were due to endogenous reactivation, and two patients had exogenous infection in our cohort. A systematic review by Yosofi et al. showed a pooled proportion of relapse as 2% with the BPaL regimens.[16] Though details of the recurrences during post-treatment follow-up of patients on BPaL regimen are available, there are limited evidences regarding relapse or reinfection based on gene sequencing /spoligotyping. Looking into the details of endogenous reactivation and exogenous infection in these patients with recurrence might help to understand the effectiveness of the regimen in a better way. Comparable recurrence free cure at the end of 48 weeks of post treatment follow up in structured dose reduction arms (9 weeks linezolid 600 mg /17 weeks linezolid 300 ng and 13 weeks linezolid 600 mg/13 weeks linezolid 300 mg) to linezolid 600 mg for 26 weeks suggest the possibility of its usage in highly resistant TB patients to avoid limiting toxicities of linezolid such as anemia and peripheral neuropathy. Most of the recurrences occurred within the first 24 weeks post treatment similar to other evidences.[17] The World Health Organization (WHO) currently recommends follow up of patients with DR TB for two years after treatment completion for early diagnosis and management of recurrent TB. Close monitoring of patients with DR TB treated with BPaL regimens especially during the first year post treatment is crucial for early detection of recurrence, appropriate management and prevention of DR TB transmission.

Table 4
Predictors of unfavorable treatment outcome at the end of 48 weeks of post-treatment follow-up.

Predictors for Unfavorable Outcome (N=378)									
Variables		Unadjusted analysis				Adjusted analysis			
		Exp (B)	95% CI for Exp (B)		p-value	Exp (B)	95% CI for Exp (B)		p-value
			Lower	Upper			Lower	Upper	
Baseline characteristics									
Gender	Female	1.79	0.97	3.29	0.06	1.82	0.82	4.03	0.14
	Male	Reference				Reference			
Age	> 30 yrs	0.75	0.42	1.35	0.320				
	≤ 30 yrs	Reference							
Weight	≤ 45 kg	1.3	0.72	2.35	0.39				
	> 45 kg	Reference							
BMI	< 16 kg/m^2	1.3	0.59	2.87	0.510				
	16–18.5 kg/m^2	0.89	0.43	1.81	0.740				
	≥18.5 kg/m^2	Reference							
Previous History of ATT	Yes	2.08	1.06	4.07	0.03	1.23	0.59	2.58	0.59
	No	Reference				Reference			
Smoking	Yes	1.5	0.72	3.14	0.28				
	No	Reference							
Alcohol	Yes	1.58	0.78	3.21	0.21				
	No	Reference							
Diabetic	Yes	1.09	0.5	2.36	0.83				
	No	Reference							
Zones	≤3	0.62	0.33	1.16	0.13	1.40	0.62	3.19	0.42
	> 3	Reference				Reference			
Lateral	Bilateral	1.57	0.81	3.08	0.19	1.48	0.60	3.62	0.39
	Unilateral	Reference				Reference			
Cavity	Yes	0.98	0.54	1.76	0.93				
	No	Reference							
Response to treatment									
Culture Conversion < 9wks during Rx	No	0.39	0.21	0.74	< 0.0001	0.42	0.2	0.87	0.02
	Yes	Reference				Reference			
Weight 5 kg increased during Rx	No	2.83	1.3	6.15	< 0.0001	0.31	0.13	0.74	0.01
	Yes	Reference				Reference			

Earlier reports have shown that lineages 1 and 3 are commonly observed in India, lineage 1 in the southern part and 3 in the central and northern regions; lineages 2 and 3 were commonly associated with drug resistance patterns.[18–20] Comparison of earlier BPaL trials done by Juliano Timm et al. reported acquired resistance to bedaquiline and pretomanid, however it was not reported for linezolid.[21] They also observed that the overall bedaquiline acquired resistance in those trials was lesser (0·45% to 1%) compared to bedaquiline-based regimens with more number of drugs (2·2%). Also, lower rates of acquired resistance for pretomanid was also observed in those trials. None of the patients in our cohort had acquired resistance to bedaquiline, pretomanid and linezolid at the time of recurrence. These evidences strengthen the implementation plan of BPaL-based regimens in the National Programmes for the management of highly drug-resistant forms of TB. However, the effectiveness of BPaL regimen in patients previously exposed to these drugs and its impact on recurrence needs to be studied. Also, it will be worthwhile to look into the role of lineages in acquiring drug resistance to bedaquiline, pretomanid and linezolid, especially in high-burden settings.

None of the baseline characteristics including age, nutritional status, and extent of the lung lesions was predictive of unfavorable treatment outcomes at the end of post-treatment follow-up. However, culture conversion beyond nine weeks of treatment and weight gain of less than five kg. from baseline were indicators of unfavorable treatment outcome. Male gender, poor nutritional status, aged 45 years and above, HIV TB co infection were identified as some of the risk factors for poor treatment outcomes at the end of treatment for a cohort of MDR TB patients in three states in India between 2009 and 2011.[22] Baseline weight above 50 kg, more number of anti TB medications, treatment with bedaquiline were shown to be independent factors predictive of survival in a South African cohort.[23] Regarding regimens consistent with fewer drugs (BPaL) given for a shorter duration of time, identifying predictors that could indicate the need for a longer duration of treatment for better treatment outcomes is essential. Lower levels of acquired resistance to bedaquiline and linezolid, as per the evidences from other BPaL-based trials, and our trial assures their availability in retreatment of most of these patients if needed. Resistance to oral agents such as ethambutol, ethionamide and pyrazinamide observed in our cohort limits their availability in subsequent management.

Regarding linezolid-related toxicities, especially with a focus on myelosuppression and peripheral neuropathy, most of the events that had occurred during treatment had resolved. None of the patients in arm 2 had any ongoing event at the end of post-treatment follow-up. Any one linezolid-associated persistent adverse event at the end of 48 weeks post-treatment follow-up was observed in 6 patients (arm 1–2 and arm 3–4). Evidences suggest that switching to lower doses of linezolid might result in better tolerance and fewer recurrent adverse events.[24] Also, this could probably be due to the close follow-up of patients and earlier interventions such as dose reduction, permanent discontinuation, temporary withholding of linezolid and appropriate management of the event in a trial setting.

Strengths of our trial included conduct of the trial in pragmatic settings in multiple sites, participant follow-up for 48 weeks post-treatment, genotyping at baseline and at the time of recurrence for understanding relapses and reinfection in our cohort. Few factors during treatment were identified as predictors of unfavorable responses. The study was not powered to look at predictors for treatment outcome, and hence, the association could not be made emphatically.

Conclusion

The structured dose reduction arms had similar recurrence-free cure rates as the linezolid 600 mg arm when given along with bedaquiline and pretomanid. Post-treatment follow-up of patients on BPaL-based regimen during the first one year is vital, as most of the recurrences occurred within the first six months. The observation of nil acquired resistance to bedaquiline, pretomanid and linezolid among patients with recurrence may suggest considering the usage of these drugs in the subsequent regimen; however, it will need future studies. Culture conversion at nine weeks of treatment and weight gain could be indicators of a favorable response to treatment.

mBPaL team

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Trial sponsors

ICMR-National Institute for Research in Tuberculosis designed the study, coordinated the data collection, and was involved in data analysis, interpretation of the data, writing reports and the decision to submit the journal for publication.

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Author contributions

CPP, BD, SS, BR, MV: conceptualization, Data Curation: RM, MB, AK, PP, AJ, PJ, CK,VK,NS, SK, JD, PV, AB, SK, RP, GT, RM, RK, DR, NN, AS, MV, CPR SK,JB, Formal Analysis: BD, CPP, CPR, MV,SS, Funding Acquisition: CPP, BR, BD, JJ, Investigation: SS, DR, NN, Methodology: CPP, BD, RB, SS, CPR MV, SK, JB, RR, SM, Project Administration: CPP, BD, BR, Supervision: CK, VO,NS, SK,JD, PV, AB, SK,RP, Visualization: CPP, BD, SS, BR, MV, Original draft was written by: BD, CPP, SS, MV, BR. All authors had full access to the data, reviewed and edited the manuscript, and accept responsibility to submit for publication.

Conflicts of interest

JJ is an employee of The UNION. All other authors report no potential conflicts of interest.

Data availability

Qualified researchers can request access to study-related documents (including the study protocol and statistical analysis plan) that support the methods and findings reported in this article. Individual participant data that underlie the results reported in this article, after de-identification, may be granted to qualified academic researchers as per ICMR–NIRT and mBPaL study data sharing policies, and subject to appropriate data sharing and transfer agreements. Requests for data should include rationale and the relevance of the proposed research, hypothesis, research methodology, statistical analysis plan and publication plan, and sent to belladevalleenal.d@icmr.gov.in.

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