Efficacy of Bedaquiline, Pretomanid, Moxifloxacin & PZA (BPaMZ) Against DS- & MDR-TB

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Abstract

Background

New anti-tuberculosis (TB) regimens are needed to treat drug sensitive (DS) and multi-drug resistant (MDR) TB. NC-005 is an ongoing Phase 2b open-label, partly randomized trial investigating the bactericidal activity of combinations of bedaquiline ($B_{loading\ dose/t.i.w.}$ or B_{200mg}), pretomanid (Pa_{200mg}), moxifloxacin (M_{400mg}), and pyrazinamide (Z_{1500mg}) in the first 8 weeks of treatment of DS-TB or MDR-TB.

Methods

Newly diagnosed patients with DS or MDR, smear positive pulmonary TB were enrolled. DS-TB patients were randomized to receive either $B_{loading\ dose/t.i.w.}PaZ$, $B_{200mg}PaZ$, or HRZE. MDR-TB patients received $B_{200mg}PaMZ$ (BPaMZ). The primary outcome was bactericidal activity measured by the rate of change in time to sputum culture positivity (TTP) over 8 weeks of treatment. Upon treatment completion, all patients were referred to the local community TB clinic for treatment according to National TB Guidelines and were scheduled to attend regular follow-up visits for 24 months. Safety was assessed by monitoring the incidence and severity of treatment emergent adverse events (TEAEs).

Results

Between 23 October 2014 and 6 May 2016, 180 patients with DS-TB and 60 patients with MDR-TB were enrolled at 10 sites in South Africa, Tanzania, and Uganda. 218 patients completed treatment and were followed through the Day 140 follow-up visit. Among all treatment arms, BPaMZ showed the highest bactericidal activity as assessed by TTP for Days 0-56 (**5.302**, 95% BCI [4.518; 6.157]), followed by that of $B_{200mg}PaZ$ (**5.223**, 95% BCI [4.526; 5.947]), $B_{loading\ dose/t.i.w.}PaZ$ (**4.906**, 95% BCI [4.274; 5.585]) and HRZE (**4.016**, 95% BCI [3.520; 4.499]). The differences in bactericidal activity of BPaMZ, $B_{200mg}PaZ$, and $B_{loading\ dose/t.i.w.}PaZ$ treatment arms versus HRZE were statistically significant. While 81.7% of patients had at least one TEAE, only 5 patients (2.1%) had a serious drug-related TEAE (2 in $B_{loading\ dose/t.i.w.}PaZ$, 2 in BPaMZ, and 1 in HRZE). Long-term safety follow-up out to 24 months post-treatment completion is ongoing.

Conclusions

The BPaMZ regimen in MDR-TB patients resulted in the highest level of bactericidal activity among all treatment arms. The BPaZ regimen was well tolerated and showed significantly higher bactericidal activity in DS-TB patients compared to HRZE. BPaZ and BPaMZ represent promising, simplified regimens to treat both DS-TB and MDR-TB.

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Background

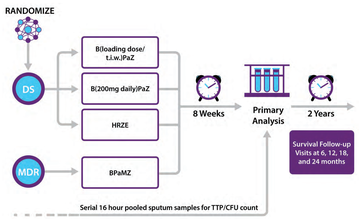
Major obstacles to successful TB management include long treatment duration, poor adherence, and concurrent HIV infection. A growing concern is the increasing identification of drug-resistant *Mycobacterium tuberculosis* (*M. tb*) isolates that require longer and more expensive treatments that have a lower overall success rate. In order to combat TB, new drugs or regimens are needed that can shorten treatment and manage drug resistant TB without the frequency of intolerance and adverse events seen with existing regimens.[1-3]

Faced with this urgent need, we have focused on the identification of novel drug combinations that can effectively treat both DS-TB and MDR-TB.

Study Design

This phase 2, multi-center, open-label, partly randomized clinical trial assessed the efficacy, tolerability, and safety of combinations of bedaquiline (B), pretomanid (Pa), and pyrazinamide (Z) regimens with and without moxifloxacin (M) during 8 weeks of treatment in patients with DS or MDR sputum smear-positive pulmonary TB.

Figure 1. 8-Week SSCC Study of BPaMZ
B, Pa, M, and Z Containing Regimens
Participants with newly diagnosed smear positive DS- and MDR-TB



Z = pyrazinamide 1500mg daily, **M** = moxifloxacin 400mg daily, **Pa** = Pretomanid 200mg daily, $B_{(registered\ dosing)}$ = bedaquiline 400mg for 14 days then 200mg three times a week, $B_{(200mg\ daily)}$ = bedaquiline 200mg daily, **HRZE** = isoniazid, rifampicin, Z, and ethambutol, **SSCC** = serial sputum colony counting

We recruited patients from seven sites in South Africa, two sites in Tanzania, and one site in Uganda. We included patients with HIV to represent the broad population of patients with pulmonary TB. Patients with HIV were eligible if their CD4+ count was greater than 100 cells per µl, they had no AIDS-defining disorder besides TB, and were not currently treated with or did not need to initiate antiretroviral therapy (ART) which is not compatible with bedaquiline. Safety assessments included history, physical examination, and vital signs, in addition to assessment of full blood counts, clinical chemistry, urinalysis, hepatic function assessment, and 12 lead ECG. 180 patients with DS-TB were randomly assigned to treatment groups, and 60 MDR-TB patients were non-randomly assigned to the BPaMZ regimen.

The primary efficacy endpoint was bactericidal activity characterized by the rate of change in time to sputum culture positivity (TTP) over 8 weeks (Days 0-56) of treatment in the Mycobacterial Growth Indicator Tube system, represented by the model-fitted log(TTP) results as calculated by the regression of the observed log(TTP) results over time. This study is registered with ClinicalTrials.gov, number NCT02193776.

Results

Patients were predominantly male and black and 53 (22%) were HIV positive. The MDR-TB group had a higher number of HIV positive patients (41.7%) as compared to the three DS-TB groups (13.6%-16.7%). Apart from resistance to rifampicin and HIV status, patient characteristics did not differ significantly between groups.

Table 1. Key Demographics
Safety Analysis Population

	B(loading) PaZ	B(200mg) PaZ	BPaMZ (MDR)	HRZE
Randomized (n)	59	60	60	61
Mean Age	35	34	34	33
Male (%)	76	80	72	75
Mean Weight (kg)	56	54	51	53
HIV + (%)	14	17	42	16
PZA Resistant* n (%)	2 (3.4)	3 (5.0)	21 (36)	2 (3.3)

* Based on pncA Sequencing

The bactericidal activity for all experimental regimens was significantly greater than that of the HRZE regimen as assessed by TTP for Days 0-56. The greatest increase in bactericidal activity was observed for the $B_{200}PaZ$ regimen with DS-TB patients and the BPaMZ regimen with MDR-TB patients.

Table 2. Bactericidal Activity (BA) Expressed As the Daily Percentage Change in Time to Positive (TTP) Signal in Liquid Culture for M. Tuberculosis (Days 0-56)

	Overnight Sputum
B(loading)PaZ	4.9
B(200mg)PaZ	5.2
BPaMZ (MDR) Z sensitive	5.3
HRZE control	4.0

The mean daily rate of change in log(CFU) counts for the BPaMZ regimen with MDR patients was significantly greater than the control HRZE with DS patients for Days 0-56.

Table 3. BA Measured As the Daily Rate of Change in log10 CFUs (Colony Forming Units) of M. Tuberculosis in Sputum on Solid Media (Days 0-56)

	Overnight Sputum
B(loading)PaZ	0.13
B(200mg)PaZ	0.12
BPaMZ (MDR) Z sensitive	0.19*
HRZE control	0.12

*The difference compared to HRZE is statistically significant.

Results *(cont)*

Table 4. Percentage of Patients Culture Negative at 2 Months
Kaplan-Meyer Analysis

	Growth Medium	
	Liquid	Solid
	Overnight	Overnight
B(loading)PaZ	66%	89%
B(200mg)PaZ	75%*	84%
BPaMZ (MDR) Z-sensitive	96%*	100%*
BPaMZ (MDR) Z-resistant	78%*	95%*
HRZE control	51%	86%

* The difference compared to HRZE is statistically significant.

The hazard ratios for time to culture negativity in liquid culture for all experimental treatment groups were different from HRZE, and these differences were statistically significant. Out of the 60 patients with MDR-TB, 38 patients had MDR-TB susceptible to Z and 22 patients had MDR-TB resistant to Z. The hazard ratios for liquid and solid culture for both Z-sensitive and Z-resistant patients in the MDR-TB treatment group were significantly different from HRZE, and these differences were also statistically significant.

Table 5. Hazard Ratios (vs HRZE) for Time to Culture Negativity Results

	Hazard Ratio vs HRZE	
	Liquid Culture	Solid Culture
B(loading)PaZ	1.7* (1.1 – 2.8)	1.3 (0.9 – 1.8)
B(200mg)PaZ	2.0* (1.3 – 3.2)	1.1 (0.8 – 1.6)
BPaMZ (MDR) Z-sensitive	3.5* (2.1 – 5.6)	2.2* (1.5 – 3.2)
BPaMZ (MDR) Z-resistant	2.0* (1.1 – 3.4)	2.6* (1.5 – 4.6)
HRZE control	--	--

* The difference compared to HRZE is statistically significant.

Z-susceptible patients did, however, perform better than Z-resistant patients.

Table 6. Hazard Ratio for Time to Culture Negativity (vs Z-resistant) for Z-susceptible MDR Group

MDR Patients	Hazard Ratio (for Liquid Culture)
BPaMZ: Z-susceptible vs Z-resistant	1.70 (1.0 – 3.0)

Most patients (196 [81.7%]) had at least one TEAE. Among the DS-TB groups, the number of patients with at least one TEAE event was similar for the $B_{200}PaZ$ and HRZE groups (75.0% and 72.1% respectively) and slightly higher for the $B_{loading\ dose}PaZ$ group (84.7%). The BPaMZ group had the highest percentage of patients with at least one TEAE (95.0%). Six patients died, with three deaths due to a TEAE. Of the three TEAE deaths, one patient was in the HRZE (control) group, and the death was deemed unlikely related to the HRZE regimen by the investigator. The second TEAE death was in the $B_{200}PaZ$ treatment group, and the third was in the $B_{loading\ dose}PaZ$ treatment group. Both of the TEAE deaths in experimental treatment groups were deemed not related to treatment by the investigator.

Results *(cont)*

Table 7. Key Safety Findings
Safety Analysis Population

	B(loading) PaZ	B(200mg) PaZ	BPaMZ (MDR)	HRZE
Randomized (n)	59	60	60	61
n (%) with at least one treatment-emergent* AE	50 (84.7)	45 (75.0)	57 (95.0)	44 (72.1)
n (%) with at least one treatment-emergent* SAE	4 (6.8)	3 (5.0)	4 (6.7)	4 (6.6)
n (%) with at least one treatment-emergent* AE leading to death	1 (1.7)	1 (1.7)	0	1 (1.6)
n (%) all deaths	1 (1.7)	1 (1.7)	3 (5.0)	1 (1.6)

*Treatment-emergent: events which started or worsened on or after the first study drug administration up to and including the Day 70 Follow-up visit (or up to and including 14 days after last study drug administration for patients not having the Day 70 Follow-up visit).

The incidence of patients with ALT and AST > 3 x ULN was lower for the HRZE treatment group compared to the other treatment groups (approximately half). The incidence of patients with ALT and AST > 10 x ULN was similar in the HRZE and BPaMZ treatment groups.

Table 8. Treatment-Emergent Hepatic AEs
Percentage of Subjects; Safety Analysis Population

	Hepatic AEs	Hepatic SAEs
B(loading)PaZ	10.2%	3.4%
B(200mg)PaZ	11.7%	0%
BPaMZ (MDR)*	15.0%	3.3%
HRZE control	4.9%	3.3%

	AST or ALT > 3x ULN	AST or ALT > 10x ULN
B(loading)PaZ	10.3%	5.2%
B(200mg)PaZ	6.7%	5.0%
BPaMZ (MDR)*	8.3%	1.7%
HRZE control	4.9%	1.6%

*BPaMZ (MDR) combines both Z-sensitive and Z-resistant MDR-TB patients.

Across the four treatment groups the highest mean change from baseline in QTcB and QTcF was observed in BPaMZ treatment group. Within the other experimental treatment groups the magnitude of the mean change from baseline in QTcB and QTcF at all visits is similar to that observed in BPaMZ treatment group and higher than the mean change associated with HRZE treatment. The change from baseline in both QTcB and QTcF for all of the experimental groups was statistically significantly higher than that of the HRZE control treatment group.

Table 9. Change From Baseline in QTcF Interval
Tukey HSD Analysis

	Mean Change (msec)	95% Confidence Interval
B(loading)PaZ	21.9	18.2 – 25.7
B(200mg)PaZ	20.4	15.1 - 25.7
BPaMZ (MDR)*	21.9	18.7 – 25.0
HRZE control	10.2	7.0 – 13.4

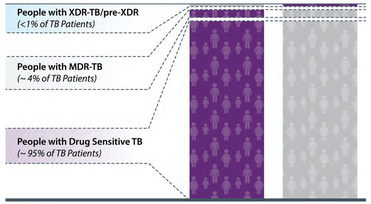
*BPaMZ (MDR) combines both Z-sensitive and Z-resistant MDR-TB patients

Discussion

This trial was the first to study a novel multidrug antituberculosis regimen, consisting of bedaquiline, pretomanid, and pyrazinamide for DS-TB patients and bedaquiline, moxifloxacin, pretomanid, and pyrazinamide for MDR-TB patients during the first 8 weeks of treatment. The primary efficacy variable, the rate of change in time to sputum culture positivity (TTP) was significantly better for patients receiving the experimental treatments than for those receiving HRZE, the current standard treatment. The percentage of patients who were sputum culture-negative after 8 weeks of treatment was significantly higher for the BPaMZ regimen with MDR-TB patients than for HRZE with DS-TB patients on both solid and liquid media. In addition, the percentage of patients who were sputum culture-negative after 8 weeks of treatment was significantly higher for the $B_{200}PaZ$ regimen on liquid culture compared to the HRZE group. In this study, dosing bedaquiline at 200 mg daily appeared to be at least as active and safe as giving the loading dose for bedaquiline, showing the potential to simplify treatment.

The results of this 8 week treatment study are consistent with the previous 14 day early bactericidal activity study [4] and show that the BPaZ regimen has mycobactericidal activity greater than that of the standard HRZE regimen. The BPaZ regimen might have potential future advantages over the present standard of care for drug-susceptible tuberculosis. The BPaMZ regimen could help rationalize and dramatically improve TB treatment by offering countries a single, 4-6 month, injection-free regimen that could treat the vast majority (perhaps 99%) of patients (see **Figure 2**).

Figure 2. A Paradigm Shift to a Novel Solution for All TB



*L = linezolid

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