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No *in vitro* synergistic effect of bedaquiline combined with fluoroquinolones, linezolid, and clofazimine against extensively drug-resistant tuberculosis

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ABSTRACT

Purpose: We explored the potential synergistic effect of bedaquiline (BDQ) combined with moxifloxacin (MFX), gatifloxacin (GAT), clofazimine (CLO), and linezolid (LZD) for treatment of extensively drug-resistant tuberculosis (XDR-TB).
Methods: Of 191 XDR-TB isolates, 20 exhibiting minimal inhibitory concentration (MIC) values ≥0.063 μg/mL for BDQ were selected to study potential synergistic, additive, or antagonistic drug effects using a checkerboard assay.
Results: Antagonism occurred in 14 (70.0%), 0 (0.0%), 13 (65.0%), and 4 (20.0%) XDR-TB isolates for BDQ-MFX, BDQ-GAT, BDQ-LZD, and BDQ-CLO combinations, respectively.
Conclusion: Our *in vitro* data demonstrate no observed synergistic effects against XDR-TB for drug combinations that included BDQ in combination with MFX, GAT, LZD, or CLO.

1. Introduction

Multidrug-resistant tuberculosis (MDR-TB), especially extensively drug-resistant tuberculosis (XDR-TB), is an important threat to TB control worldwide (WHO, 2016). Given widespread broad antibiotic resistance to fluoroquinolone (FQ) and any second-line antituberculosis injectable drugs (SLIDs), treatment options for XDR-TB are limited and achieve worse treatment outcomes as compared with outcomes of MDR-TB treatment (Caminero et al., 2010). In a recent meta-analysis, the success rate of patient treatment for XDR-TB infection approached only 44%, with mortality varying from 14% to 27% (Jacobson et al., 2010). Thus, the devastating consequences associated with XDR-TB highlight an urgent need for novel antimicrobial agents to curtail the global XDR-TB epidemic (Gandhi et al., 2010).

Bedaquiline (BDQ) is the first anti-TB agent approved by the US Food and Drug Administration within the past 40 years for treatment of MDR-TB (Cox and Laessig, 2014; Pang et al., 2017a). BDQ inhibits ATP biosynthesis by acting on ATP synthase subunit C (Pang et al., 2017a). Previous studies have demonstrated that BDQ shows potent activity against both drug-susceptible and drug-resistant *Mycobacterium tuberculosis* (MTB) isolates in both *in vitro* and *in vivo* experiments (Andries et al., 2005). A series of clinical trials has further confirmed the impressive efficacy of BDQ for treatment of patients infected with M/XDR-TB (Diacon et al., 2012; Pontali et al., 2016). On the basis of data and clinical experience of BDQ use within the past few years, the World Health Organization (WHO) recommends that BDQ be added to a WHO-recommended regimen for the treatment of M/XDR-TB (WHO, 2015). Despite this endorsement for BDQ use for MDR-TB treatment, recent controversies have emerged concerning whether BDQ should be provided to all MDR-TB patients. Specifically, the continued susceptibility of MDR-TB bacilli to FQs and/or SLIDs suggests that BDQ would provide greater benefit to XDR-TB patients than to those with MDR-TB (Dheda et al., 2017a). Therefore, it would be meaningful to investigate the interaction between BDQ and other drugs in various drug combinations for XDR-TB treatment since limited data have been reported on this topic (Reddy et al., 2010). In our most recent work, we analyzed *in vitro* drug susceptibility of BDQ, moxifloxacin (MFX), gatifloxacin (GAT), linezolid (LZD), and clofazimine (CLO) against XDR-TB (Pang et al.,

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2017b). Here we extend those *in vitro* experiments to discover the potential synergistic effects of BDQ combined with MFX, GAT, CLO, and LZD against XDR-TB.

2. Materials and methods

2.1. Bacterial isolates

In vitro susceptibility testing was conducted for a total of 191 XDR-TB isolates using a broth microdilution method as described previously (Pang et al., 2017b). XDR-TB isolates were identified by reviewing *in vitro* drug susceptibility testing (DST) results performed by the National TB Clinical Laboratory. In total, 8 drugs were used to conduct conventional DST, including rifampicin (RIF), isoniazid (INH), streptomycin (SM), ethambutol (EMB), capreomycin (CPM), amikacin (AMK), ofloxacin (OFLX), and levofloxacin (LFX). MDR-TB was defined as resistance to both RIF and INH. XDR-TB was defined as resistance to RIF and INH with additional resistance to OFLX and/or LFX and at least 1 injectable second-line drug including CPM, kanamycin (KM), and/or AMK.

2.2. Minimal inhibitory concentration

We used the Alamar Blue assay to conduct minimal inhibitory concentration (MIC) determinations of XDR-TB identified previously by conventional drug susceptibility testing (Pang et al., 2017b). Briefly, fresh bacterial clones were harvested from Löwenstein–Jenson slants. Next, the turbidity of each suspension was adjusted to equal the 1.0 McFarland standard. After dilution with Middlebrook 7H9 broth containing 10% OADC, 100 μL of this inoculum was added to wells of 96-well plates containing corresponding drugs. After 7 days of incubation, Alamar Blue reagent was added to each well. Following incubation at 37 °C for 24 h, color change was used to evaluate bacterial growth. The MIC is defined as the lowest concentration of a drug that will inhibit the color change from blue to pink. Concentrations of antibiotics used in the test panel ranged from 0.016 to 32 mg/L. In order to calculate the fractional inhibitory concentration (FIC) accurately, 20 isolates with MIC values ≥0.063 μg/mL for BDQ were selected for further drug combination testing.

2.3. Drug interaction testing

Combinations of BDQ with MFX, GAT, LZD, and CLO were used to identify potential synergistic, additive, or antagonistic effects via a checkerboard assay as previously described (Zhang et al., 2015). The assay was similar to that used for determining MICs by the broth dilution method. Serial concentrations of antimicrobial agents in combinations ranging from 1/16 times the MIC (1/16 × MIC) to 8 times the MIC (8 × MIC) were used. In addition, MIC values of each antimicrobial agent alone were confirmed by the broth microdilution method in parallel. Interpretation of data was achieved by calculating the combined FIC as follows:

$$\mathrm{FIC} = \frac{\mathrm{MIC[A]combination}}{\mathrm{MIC[A]alone}} + \frac{\mathrm{MIC[B]combination}}{\mathrm{MIC[B]alone}}.$$

Results for each drug interaction were interpreted as synergistic for an FIC index value ≤0.5, indifferent if the FIC index was between 0.5 and 2, and antagonistic if the FIC index was >2 (Zhang et al., 2015). All *in vitro* experiments were performed in triplicate. The reference MTB strain (H37Rv) was used for quality control in each batch experiment.

2.4. Statistical analysis

The Fisher's exact test was used to compare study groups with respect to proportions of MTB isolates exhibiting synergy or antagonism. All statistical analyses were performed using SPSS v. 14.0 (SPSS Inc., Chicago, IL), and differences were declared statistically significant for $P < 0.05$.

3. Results

Results of checkerboard tests between BDQ and FQs are presented in Table 1. MICs for MTB H37Rv were 0.063 mg/L for BDQ, 0.125 mg/L for MFX and GAT, 0.5 mg/L for LZD, and 0.25 mg/L for CLO. XDR-TB isolates exhibited predominately antagonistic effects for the BDQ-MFX combination (70.0% of isolates, 14/20), while all XDR-TB isolates (100.0% of isolates, 20/20) showed indifference for BDQ combined with GAT. Statistical analysis revealed that the proportion of XDR-TB isolates exhibiting antagonism for the BDQ-MFX combination was significantly higher than for the BDQ-GAT combination ($P < 0.01$). In addition, we also analyzed the synergistic effect of BDQ when combined with LZD or CLO. As shown in Table 2, antagonism occurred in 13 (65.0%, 13/20) and 4 (20.0%, 4/20) XDR-TB isolates for BDQ-LZD and BDQ-CLO combinations, respectively. Notably, no synergistic effect was noted for any agent combination.

4. Discussion

Treatment of XDR-TB, an incurable form of TB with existing drugs is still a major challenge that could benefit from development of novel drug candidates, the most promising of which is BDQ (Pontali et al., 2016). Thus, a better understanding of the interaction between BDQ and other anti-TB drugs is essential for formulating more effective chemotherapeutic regimens. In this study, our results revealed that MFX in combination with BDG exhibits antagonism for a higher proportion of XDR-TB isolates than does GAT when combined with BDQ. Conversely, a previous report from Kowalski and colleagues demonstrated that a higher proportion of isolates exhibited synergistic growth inhibition for GAT plus benzalkonium than for MFX plus benzalkonium (Kowalski et al., 2006). Here, the exact reasons for the difference in antagonism between BDQ-MFX and BDQ-GAT combinations are not known. However, one possible explanation may be due to potentially different interactions occurring between BDQ and MFX versus GAT between different media or under intracellular conditions, a hypothesis that should be investigated using *in vitro* studies. The *in vitro* findings from this study show that the MICs of BDQ for XDR-TB isolates increased after MFX addition, suggesting that MFX may attenuate BDQ activity against XDR-TB isolates. For isolates with MIC values slightly lower than the BDQ MIC breakpoint, this increase might lead to BDQ resistance. Based on the indifference effect of BDQ-GAT in our *in vitro* experiments, GAT may be a preferred agent for use in combination with BDQ against XDR-TB. Further clinical studies using animal infection models will be useful for investigating interactions between BDQ and FQs.

Despite a previous report describing synergistic anti-MTB activity observed when LZD was combined with clarithromycin and EMB (Zou et al., 2015), here an antagonistic effect toward most XDR-TB isolates was observed for BDQ-LZD combination *in vitro*. It would be interesting to explore the reason behind this antagonism. What is known is that BDQ, by binding to ATP synthase, prevents *in vivo* ATP production and stops bacterial growth (Andries et al., 2005). Meanwhile, LZD targets the formation of a functional 70S ribosomal translation initiation complex, thereby leading to failure of bacterial protein synthesis (Zou et al., 2015). Considering that protein synthesis requires abundant energy, we hypothesize that BDQ normally acts upstream of LZD in the ATP biosynthetic process and thus may attenuate LZD antibacterial activity. Another possibility is that BDQ inhibits active transport required for ATP-dependent LZD uptake by bacterial cells, which may also contribute to antagonistic effects observed between BDQ and other antimicrobial agents.

Table 1
MICs and FICIs of BDQ and FQs against XDR-TB isolates.[a]

No.	MIC (μg/mL)				FICI	Relationship	MIC (μg/mL)				FICI	Relationship
	BDQ alone	MFX alone	BDQ combination	MFX combination			BDQ alone	GAT alone	BDQ combination	GAT combination		
XDR2	0.5	0.5	2	0.5	5	A	0.5	0.25	0.25	0.25	1.5	I
XDR15	0.125	1	0.125	2	3	A	0.125	1	0.063	1	1.5	I
XDR22	0.25	0.25	0.25	0.5	3	A	0.25	0.125	0.125	0.125	1.5	I
XDR26	0.063	0.5	0.031	0.25	1	I	0.063	0.25	0.063	0.25	2	I
XDR28	0.063	0.5	0.063	1	3	A	0.063	0.25	0.031	0.25	1.5	I
XDR41	0.5	1	1	2	4	A	0.5	0.5	0.25	0.5	1.5	I
XDR56	0.125	0.5	0.25	1	4	A	0.125	0.25	0.125	0.25	2	I
XDR74	0.125	1	0.125	1	2	I	0.125	1	0.063	1	1.5	I
XDR81	0.5	2	0.5	4	3	A	0.5	2	0.25	1	1	I
XDR89	0.063	0.5	0.25	1	6	A	0.063	0.25	0.031	0.25	1.5	I
XDR91	0.25	1	0.25	2	3	A	0.25	0.5	0.125	0.5	1.5	I
XDR98	0.125	1	0.125	1	2	I	0.125	0.5	0.063	0.5	1.5	I
XDR104	0.063	0.5	0.063	1	3	A	0.063	0.25	0.063	0.25	2	I
XDR123	0.063	1	0.063	1	3	A	0.063	1	0.031	0.5	1	I
XDR136	0.25	2	0.25	4	3	A	0.25	1	0.125	1	1.5	I
XDR153	0.125	0.25	0.125	0.25	2	I	0.125	0.063	0.063	0.063	1.5	I
XDR168	0.125	0.5	0.125	0.5	2	I	0.125	0.25	0.125	0.25	2	I
XDR176	0.5	1	1	1	3	A	0.5	0.5	0.25	0.5	1.5	I
XDR179	0.125	0.5	0.125	0.5	2	I	0.125	0.25	0.063	0.25	1.5	I
XDR185	0.063	0.25	0.063	0.5	3	A	0.063	0.25	0.031	0.25	1.5	I
H37Rv	0.063	0.125	0.063	0.25	3	A	0.063	0.125	0.031	0.125	1.5	I

[a] BDQ, bedaquiline; MFX, moxifloxacin; GAT, gatifloxacin; MIC, minimal inhibitory concentration; FICI, fractional inhibitory concentration index; S, synergism; I, indifference; A, antagonism. ($P<0.01$).

We must acknowledge several limitations of this study. First, synergistic effects observed *in vitro* may not always mirror *in vivo* effects. Thus, further *in vivo* studies using animal models will be carried out to expand our knowledge regarding *in vivo* effects of combinations of BDQ and other antimicrobial agents. Second, another major limitation stems from the small number of MTB isolates studied here that reflects the extremely low prevalence of BDQ resistance among MTB isolates. Third, only XDR-TB isolates, rather than drug-susceptible and other drug-resistant MTB isolates, were evaluated in this study. Recent data from Zou et al. have reported that a lower proportion of XDR-TB isolates exhibits synergistic activity in drug combination studies as compared with MDR-TB isolates (Zou et al., 2015). Thus, the sample selection bias of the present study potentially limits generalization of results to all TB isolates. Therefore, additional studies are needed to expand our knowledge of antagonistic mechanisms of combinations of BDQ with other antimicrobials against drug-susceptible and MDR-TB isolates. Fourth, given that BDQ could inhibit both actively replicating MTB as well as the nonreplicating dormant population (Cox and Laessig, 2014), it would be interesting to investigate *in vitro* synergistic effects between BDQ and other agents against dormant bacilli. Unfortunately, *in vitro* models of MTB nonreplicating persistent cells have not yet been established. Despite these limitations, our preliminary data have important implications for the clinical use of BDQ for XDR-TB treatment. On the one hand, depending on availability and prior resistance profiles, the current XDR-TB regimen in many countries consists of a backbone of BDQ, LZD, and CLO as core drugs (Dheda et al., 2017b). The infrequent antagonistic interaction between BDQ and CLO highlights that this combination should be useful for treatment of patients infected with

Table 2
MICs and FICIs of BDQ and LZD, CLO against XDR-TB isolates.

No.	MIC (μg/mL)				FICI	Relationship	MIC (μg/mL)				FICI	Relationship
	BDQ alone	LZD alone	BDQ combination	LZD combination			BDQ alone	CLO alone	BDQ combination	CLO combination		
XDR2	0.5	0.5	0.5	0.5	2	I	0.5	2	0.5	1	1.5	I
XDR15	0.125	0.25	0.125	0.5	3	A	0.125	1	0.125	0.5	1.5	I
XDR22	0.25	0.25	0.5	0.5	4	A	0.25	2	0.5	1	2.5	A
XDR26	0.063	0.125	0.031	0.125	1.5	I	0.063	0.5	0.063	0.25	1.5	I
XDR28	0.063	0.25	0.063	0.5	3	A	0.063	0.063	0.125	0.031	1.5	I
XDR41	0.5	0.5	0.5	1	3	A	0.5	4	0.5	2	1.5	I
XDR56	0.125	0.25	0.25	0.5	4	A	0.125	0.5	0.125	0.5	3	A
XDR74	0.125	0.5	0.063	0.5	1.5	I	0.125	1	0.125	0.5	1.5	I
XDR81	0.5	1	1	1	3	A	0.5	4	0.5	1	1.25	I
XDR89	0.063	0.25	0.063	0.5	3	A	0.063	1	0.063	0.25	1.25	I
XDR91	0.25	0.5	0.125	0.5	1.5	I	0.25	2	0.25	1	1.5	I
XDR98	0.125	0.25	0.25	0.25	3	A	0.125	1	0.125	0.5	1.5	I
XDR104	0.063	0.125	0.125	0.25	4	A	0.063	2	0.125	1	2.5	A
XDR123	0.063	0.25	0.063	0.25	2	I	0.063	1	0.063	1	2	I
XDR136	0.25	1	0.5	1	3	A	0.25	4	0.25	2	1.5	I
XDR153	0.125	0.25	0.125	0.25	2	I	0.125	1	0.125	0.5	1.5	I
XDR168	0.125	0.5	0.25	0.5	3	A	0.125	0.25	0.125	0.25	2	I
XDR176	0.5	0.25	0.5	0.5	3	A	0.5	0.5	0.5	0.25	1.5	I
XDR179	0.125	0.125	0.063	0.25	2.5	A	0.125	2	0.125	1	1.5	I
XDR185	0.063	0.125	0.063	0.125	2	I	0.063	0.5	0.125	0.25	2.5	A
H37Rv	0.063	0.5	0.063	0.5	2	I	0.063	0.25	0.063	0.25	2	I

BDQ = bedaquiline; LZD = linezolid; CLO = clofazimine; MIC = minimal inhibitory concentration; FICI = fractional inhibitory concentration index; S = synergism; I = indifference; A = antagonism ($P=0.010$).

XDR-TB. On the other hand, antagonistic effects observed for the BDQ-LZD combination against more than half of XDR-TB isolates tested in this study suggests that caution is warranted when considering aggressive empirical treatment incorporating the BDQ-LZD combination for use against XDR-TB.

In conclusion, our *in vitro* data demonstrate that no synergistic anti-XDR-TB effect was observed for BDQ in combination with MFX, GAT, or LZD, with MFX-BDQ shown to be more antagonistic than GAT-BDQ. Further studies are needed to confirm these findings and to evaluate therapeutic regimens incorporating BDQ for use against XDR-TB.

Author contributions

- NC and HH designed the study. YP, WJ, and ZZ conducted the experiment. YP, WJ, and JL wrote the manuscript. FH, LD, GD, and YL participated in data collection. All authors approved the final version of the paper.

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Compliance with ethical standards

Conflict of interest

The authors declare that they have no competing interests.

Ethical approval

This study was approved by the Ethic Committee of Beijing Chest Hospital affiliated to Capital Medical University.

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