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SUSCEPTIBILITY

In Vitro Activity of Bedaquiline and Delamanid against Nontuberculous Mycobacteria, Including Macrolide-Resistant Clinical Isolates

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ABSTRACT We evaluated the *in vitro* activities of the antimicrobial drugs bedaquiline and delamanid against the major pathogenic nontuberculous mycobacteria (NTM). Delamanid showed high MIC values for all NTM except *Mycobacterium kansasii*. However, bedaquiline showed low MIC values for the major pathogenic NTM, including *Mycobacterium avium* complex, *Mycobacterium abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. kansasii*. Bedaquiline also had low MIC values with macrolide-resistant NTM strains and warrants further investigation as a potential antibiotic for NTM treatment.

KEYWORDS *Mycobacterium abscessus*, *Mycobacterium avium* complex, *Mycobacterium kansasii*, bedaquiline, delamanid, nontuberculous mycobacteria

The incidence and prevalence of pulmonary disease (PD) associated with nontuberculous mycobacteria (NTM) are increasing worldwide (1, 2). *Mycobacterium avium* complex (MAC), *Mycobacterium abscessus*, and *Mycobacterium kansasii* are the most common pathogens for NTM PD worldwide (3–5). Macrolide antibiotics, such as clarithromycin and azithromycin, are key drugs for treating NTM PD, especially MAC PD (1, 2). Treatment outcomes are still not satisfactory (6–9), however, and the development of acquired resistance to macrolides can further worsen treatment outcomes (10, 11). Moreover, *M. abscessus* isolates can have intrinsic inducible macrolide resistance or acquired macrolide resistance, and *M. abscessus* PD is the most difficult-to-treat type of NTM PD (12–14). Therefore, discovery of new and repurposed drugs is urgently needed (15).

Bedaquiline and delamanid are new drugs for the treatment of multidrug-resistant tuberculosis (16–20). Bedaquiline is a diarylquinoline that inhibits the proton pump of mycobacterial ATP synthase, and delamanid is a compound derived from nitrodihydroimidazooxazole that inhibits mycolic acid synthesis (21–23). Previous studies reported that the MICs of bedaquiline and delamanid for *Mycobacterium tuberculosis*, including multidrug-resistant isolates, were very low (24, 25).

Recently, the MICs of bedaquiline against MAC, including *M. avium* and *Mycobacterium intracellulare*, have been reported (26–28). In those studies, most macrolide-sensitive MAC isolates showed low MICs for bedaquiline (26–28). In addition, *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* have low MIC values for bedaquiline (28–30).

Citation Kim DH, Jhun BW, Moon SM, Kim S-Y, Jeon K, Kwon OJ, Huh HJ, Lee NY, Shin SJ, Daley CL, Koh W-J. 2019. *In vitro* activity of bedaquiline and delamanid against nontuberculous mycobacteria, including macrolide-resistant clinical isolates. Antimicrob Agents Chemother 63:e00665-19. https://doi.org/10.1128/AAC.00665-19.

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Received 28 March 2019
Returned for modification 23 April 2019
Accepted 4 June 2019
Accepted manuscript posted online 10 June 2019
Published 25 July 2019

In contrast to those bedaquiline studies, there has been only one study on the MICs of delamanid for MAC (31), and delamanid MICs for other NTM species have not been reported. In addition, there has been no comparative analysis of MIC values for bedaquiline and delamanid with various NTM, including macrolide-resistant NTM. The purpose of the present study was to evaluate the MICs of bedaquiline and delamanid against major pathogenic NTM clinical isolates, including macrolide-resistant NTM.

For this study, which was initially approved by the institutional review board (IRB) of Samsung Medical Center in 2008 and has received IRB approval once a year (IRB approval no. 2008-09-016; last updated 2 February 2019), we included 251 clinical isolates of five major pathogenic NTM (*M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, *M. abscessus* subsp. *massiliense*, and *M. kansasii*) isolated from patients newly diagnosed with NTM PD. We also included 56 clinical isolates of acquired-macrolide-resistant NTM (*M. avium*, *M. intracellulare*, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense*), which were confirmed to have a 23S rRNA gene mutation associated with the acquisition of macrolide resistance (32–34). *In vitro* susceptibility testing with bedaquiline and delamanid was performed by measuring the MIC using the broth microdilution method, according to Clinical and Laboratory Standards Institute guidelines (35). *Mycobacterium peregrinum* ATCC 700686, *M. abscessus* ATCC 19977, *M. avium* ATCC 700898, and *M. kansasii* ATCC 12478 were used as controls.

Table 1 shows the MIC, MIC_{50}, and MIC_{90} values of bedaquiline and delamanid for 251 isolates from newly diagnosed NTM PD patients. All MAC, *M. abscessus* subsp. *massiliense*, and *M. kansasii* isolates were susceptible to macrolides; most *M. abscessus* subsp. *abscessus* isolates, except for 11 macrolide-susceptible isolates, had inducible resistance to macrolides, which was confirmed using sequence analysis of the *erm*(41) gene. MAC and *M. kansasii* isolates had very low bedaquiline MIC_{50} ($\leq$0.016 μg/ml) and MIC_{90} ($\leq$0.016 μg/ml) values. Although the *M. abscessus* subsp. *abscessus* and *M. abscessus* subsp. *massiliense* isolates also had very low bedaquiline MIC_{50} (0.062 μg/ml) and MIC_{90} (0.125 μg/ml) values, the MICs were higher than those for MAC and *M. kansasii* isolates.

In contrast, MAC, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense* isolates had very high delamanid MIC_{50} (8 to $>$16 μg/ml) and MIC_{90} ($>$16 μg/ml) values. Compared to those NTM, *M. kansasii* had relatively low delamanid MIC_{50} (0.25 μg/ml) and MIC_{90} (1 μg/ml) values.

The MIC, MIC_{50}, and MIC_{90} values for bedaquiline and delamanid with 56 isolates of macrolide-resistant NTM are shown in Table 2. All macrolide-resistant NTM isolates showed very low bedaquiline MIC_{50} ($\leq$0.016 to 0.062 μg/ml) and MIC_{90} ($\leq$0.016 to 0.25 μg/ml) values. For all macrolide-resistant NTM isolates, however, the delamanid MIC_{50} (4 to $>$16 μg/ml) and MIC_{90} ($>$16 μg/ml) values were very high (Table 2).

In this study, we evaluated the bedaquiline and delamanid MICs for major pathogenic NTM clinical isolates, including acquired-macrolide-resistant NTM isolates. Consistent with previous studies, our results showed that MAC, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense* isolates, as well as *M. kansasii* isolates, had low bedaquiline MIC_{50} and MIC_{90} values.

In particular, the low bedaquiline MICs for macrolide-resistant NTM isolates, including MAC, *M. abscessus* subsp. *abscessus*, and *M. abscessus* subsp. *massiliense* isolates, are notable in this study. Although the clarithromycin MIC_{50} and MIC_{90} values for all macrolide-resistant NTM isolates were $>$64 μg/ml, the macrolide-resistant NTM isolates showed significantly lower bedaquiline MIC_{50} ($\leq$0.016 to 0.062 μg/ml) and MIC_{90} ($\leq$0.016 to 0.25 μg/ml) values. These results suggest that bedaquiline may be an effective antimicrobial for treatment of macrolide-resistant NTM strains.

In contrast, in this study, the delamanid MICs were high for most major pathogenic NTM isolates. The exception was *M. kansasii*, for which the delamanid MIC_{50} and MIC_{90} values were relatively low, compared to the values for other NTM isolates. These results, especially the delamanid MICs for MAC isolates, differed from those of one previous study (31). Although studies on delamanid resistance have reported that five genes (*ddn*, *fgd1*, *fbiA*, *fbiB*, and *fbiC*) are associated with delamanid resistance in *M. tubercu-*

TABLE 1 MIC ranges and MIC_{50} and MIC_{90} values of bedaquiline and delamanid for 251 clinical NTM isolates

NTM species and antibiotic	No. (%) of isolates with MIC of:													
	≤0.016 μg/ml	0.031 μg/ml	0.062 μg/ml	0.125 μg/ml	0.25 μg/ml	0.5 μg/ml	1 μg/ml	2 μg/ml	4 μg/ml	8 μg/ml	16 μg/ml	>16 μg/ml	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
M. avium (54 isolates)														
Bedaquiline	50 (93)	1 (2)			2 (4)	1 (2)							≤0.016	≤0.016
Delamanid				1 (2)		2 (4)	3 (6)	5 (9)	10 (19)	13 (24)	3 (6)	17 (32)	8	>16
M. intracellulare (48 isolates)														
Bedaquiline	45 (94)		1 (2)		2 (4)								≤0.016	≤0.016
Delamanid	1 (2)						5 (10)	5 (10)	4 (8)	1 (2)	13 (27)	19 (40)	16	>16
M. abscessus subsp. *abscessus* (49 isolates)														
Bedaquiline	2 (4)	7 (14)	31 (63)	5 (10)	4 (8)								0.062	0.125
Delamanid											12 (24)	37 (76)	>16	>16
M. abscessus subsp. *massiliense* (53 isolates)														
Bedaquiline	3 (6)	21 (40)	18 (34)	6 (11)	5 (9)								0.062	0.125
Delamanid											16 (30)	37 (70)	>16	>16
M. kansasii (47 isolates)														
Bedaquiline	46 (98)				1 (2)								≤0.016	≤0.016
Delamanid		1 (2)	4 (9)	11 (23)	11 (23)	14 (30)	3 (6)	1 (2)				2 (4)	0.25	1

TABLE 2 MIC ranges and MIC_{50} and MIC_{90} values of bedaquiline and delamanid for 56 macrolide-resistant clinical NTM isolates

NTM species and antibiotic	No. (%) of isolates with MIC of:													
	≤0.016 μg/ml	0.031 μg/ml	0.062 μg/ml	0.125 μg/ml	0.25 μg/ml	0.5 μg/ml	1 μg/ml	2 μg/ml	4 μg/ml	8 μg/ml	16 μg/ml	>16 μg/ml	MIC_{50} (μg/ml)	MIC_{90} (μg/ml)
M. avium (10 isolates)														
Bedaquiline	10 (100)												≤0.016	≤0.016
Delamanid					1 (10)		2 (20)	1 (10)	1 (10)			5 (50)	4	>16
M. intracellulare (16 isolates)														
Bedaquiline	15 (94)			1 (6)									≤0.016	≤0.016
Delamanid							2 (13)		1 (6)			13 (81)	>16	>16
M. abscessus subsp. *abscessus* (12 isolates)														
Bedaquiline	3 (25)	1 (8)	4 (33)	3 (25)	1 (8)								0.062	0.125
Delamanid												12 (100)	>16	>16
M. abscessus subsp. *massiliense* (18 isolates)														
Bedaquiline	1 (6)	1 (6)	7 (39)	7 (39)	1 (6)	1 (6)							0.062	0.25
Delamanid												18 (100)	>16	>16

losis (36), a similar association has not yet been reported for NTM. Given the high delamanid MICs that we observed with MAC and *M. abscessus* clinical isolates, additional studies to identify genes that contribute to delamanid resistance in NTM are needed.

Previous studies reported that mutations within the *atpE*, Rv0678, and *pepQ* genes are involved in bedaquiline resistance in *M. tuberculosis* (37). In addition, recent studies on bedaquiline-resistance-related genes in NTM have been reported. Alexander and colleagues found that mutations in the *mmpT5* and *atpE* genes were associated with bedaquiline resistance in MAC strains (38). In addition, in *M. abscessus* subsp. *abscessus*, mutations in the *atpE* and MAB_2299c genes have been reported to be associated with bedaquiline resistance (39, 40). Therefore, if bedaquiline is used for NTM treatment, then the possibility of bedaquiline resistance due to mutation in a bedaquiline-resistance-related gene should be considered, although most NTM isolates had very low bedaquiline MIC values in this study.

In summary, we evaluated the *in vitro* activities of bedaquiline and delamanid against major pathogenic NTM clinical isolates. Our results showed that bedaquiline had good *in vitro* activity against major pathogenic NTM but delamanid did not. Bedaquiline has the potential to be a potent agent for the treatment of NTM PD, including macrolide-resistant NTM PD.

ACKNOWLEDGMENTS

This research was supported by the National Research Foundation of Korea (NRF), funded by the South Korean Ministry of Science, Information, and Communications Technologies (grant NRF-2018R1A2A1A05018309 to W.-J.K.), and by the Basic Science Research Program through the NRF, funded by the Ministry of Education (grant NRF-2016R1A6A3A11930738 to D.H.K.).

C.L.D. has received grants from Insmed, Inc., and served on advisory boards for Otsuka, Insmed, Johnson and Johnson, Spero, and Horizon, not associated with the submitted work. W.-J.K. has received a consultation fee from Insmed, Inc., for the Insmed advisory board meeting, not associated with the submitted work. Otherwise, we have no conflicts of interest to declare.

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