Poster No. 2135
IDWeek 2023
Boston, MA
October 11-15, 2023

Epetraborole in vitro activity against *Mycobacterium avium* complex recent clinical isolates from Japan

Akio Aono[1]; Yuriko Igarashi[1]; Kinuyo Chikamatsu[1]; Akiko Takaki M.D., Ph.D.[1]; Satoshi Mitarai, M.D., Ph.D.[1]; Tiffany R. Keepers, Ph.D.[2]

[1]Department of Mycobacterium Reference and Research, the Research Institute of Tuberculosis, Japan Anti-Tuberculosis Association, Tokyo, Japan; [2]AN2 Therapeutics, Inc., Menlo Park, CA, USA

AN2Therapeutics

Menlo Park, CA 94027
www.an2therapeutics.com

ABSTRACT

Background
Epetraborole (EBO) is a boron-containing, oral inhibitor of bacterial leucyl-tRNA synthetase, an essential enzyme in protein synthesis. EBO demonstrates potent activity against nontuberculous mycobacteria (NTM) and is currently under clinical development for treatment of treatment-refractory *Mycobacterium avium* complex (MAC) lung disease. The objective of this study was to evaluate the in vitro activity of EBO against recent MAC isolates from Japan.
Methods
Minimal inhibitory concentration (MIC) values for EBO, amikacin (AMK), clarithromycin (CLR), rifabutin (RFB), and ethambutol (EMB) were determined using broth microdilution assays according to Clinical and Laboratory Standards Institute M24-A3 guideline (2018) against 110 MAC clinical isolates collected from Japanese patients in 2020. MAC isolates were of respiratory origin and included 55 *M. avium* and 55 *M. intracellulare* isolates.
Results
EBO MIC values ranged from 0.25 - 16 µg/mL and the EBO MIC_{50} and MIC_{90} were 2 and 4 µg/mL, respectively (Table 1). The CLR MIC range was 0.125 – >32 µg/mL and included 4 CLR-resistant isolates (MIC ≥ 32 µg/mL). CLR MIC_{50} and MIC_{90} were 1 and 4 µg/mL, respectively. All isolates were susceptible to AMK and had an MIC range of 2 - 32 µg/mL; the MIC_{50} and MIC_{90} were 8 and 16 µg/mL, respectively. The EMB MIC range was 2 - >32 µg/mL; the MIC_{50} and MIC_{90} were 4 and 16 µg/mL, and the RFB MIC range was ≤0.03 - 2 µg/mL and MIC_{50} and MIC_{90} were 0.06 and 0.25 µg/mL. EBO maintained activity with MIC values of 0.25 - 2 µg/mL against the 4 CLR-resistant isolates.
Conclusions
EBO demonstrated potent *in vitro* activity against 110 recent MAC isolates collected from Japanese patients. Furthermore, EBO demonstrated *in vitro* activity against CLR-resistant MAC isolates suggesting that CLR-resistance does not impact EBO activity. These data are similar to results obtained against U.S. isolates and support the continued clinical evaluation of the use of EBO in the treatment of MAC lung disease in Japan.

INTRODUCTION

NTM lung disease (NTM-LD) is a rare, chronic and progressive infectious disease. The incidence and prevalence rates of NTM-LD are among the highest worldwide in Japan and rates are increasing .[1, 2] The most common causative pathogen is MAC, which causes nearly 90% of NTM-LD in Japan.[2] EBO is a boron-containing, oral inhibitor of bacterial leucyl-tRNA synthetase, an essential enzyme in protein synthesis. EBO demonstrates potent activity against NTM both in vitro and in vivo, and is currently under clinical development for treatment-refractory MAC lung disease (NCT05327803). Previous studies have shown EBO is active against MAC isolates obtained from the US with MICs ranging from 0.25 to 8 µg/mL.[3] The objective of this study was to evaluate the in vitro activity of EBO against recent MAC isolates from Japan.

METHODS

Minimal inhibitory concentration (MIC) values for EBO, amikacin (AMK), clarithromycin (CLR), rifabutin (RFB), and ethambutol (EMB) were determined using broth microdilution assays according to Clinical and Laboratory Standards Institute (CLSI) M24-A3 guideline (2018) against 110 MAC clinical isolates collected from Japanese patients in 2020. MAC isolates were of respiratory origin and included 55 *M. avium* and 55 *M. intracellulare* isolates. Broth microdilution assays were conducted using cation-adjusted Mueller-Hinton broth (CAMHB, Difco) plus 5% oleic acid-albumin-dextrose-catalase (OADC). Plates were incubated at 36 ± 1 ° C under 5% CO_2 for 7 to 10 days. MICs were determined when the growth control demonstrated sufficient growth in the plate, which within 7-10 days of incubation. Susceptibility was interpreted using CLSI interpretive criteria (M24S, 2023).

RESULTS

EBO MIC values ranged from 0.25 - 16 µg/mL and 98.2% of isolates had EBO MIC values ≤8 µg/mL (Table 1, Figure 1). The EBO MIC_{50} and MIC_{90} were 2 and 4 µg/mL, respectively. This EBO MIC distribution for MAC isolates from Japanese patients is consistent with EBO MIC distribution observed for isolates from the US (MIC range 0.25 - 8 µg/mL, MIC_{50}/MIC_{90} = 2/8 µg/mL).[3] The CLR MIC range was 0.125 - >32 µg/mL and included 4 CLR-resistant isolates (MIC ≥32 µg/mL, CLSI M24S, 2023). CLR MIC_{50} and MIC_{90} were 1 and 4 µg/mL, respectively. All isolates were susceptible to AMK (inhaled and IV breakpoints, CLSI M24S, 2023) and had an MIC range of 2 - 32 µg/mL; the MIC_{50} and MIC_{90} were 8 and 16 µg/mL, respectively. The EMB MIC range was 2 - >32 µg/mL; the MIC_{50} and MIC_{90} were 4 and 16 µg/mL, and the RFB MIC range was ≤0.03 - 2 µg/mL and MIC_{50} and MIC_{90} were 0.06 and 0.25 µg/mL. EBO MIC values were similar among *M. avium* and *M. intracellulare* species (Table 1, Figure 2). The 2 isolates with EBO MIC = 16 µg/mL were *M. avium* species. There were 4 CLR-resistant isolates, and EBO maintained activity against these isolates with MIC values of 0.25 - 2 µg/mL (Table 2).

Table 1. Epetraborole and comparator antimicrobial MIC values against 110 recent MAC clinical isolates from Japan.

Organism	Antimicrobial	MIC (µg/mL)		
		MIC Range	MIC_{50}	MIC_{90}
MAC (n=110)	Epetraborole	0.25 – 16	2	4
	Clarithromycin	0.125 – >32	1	4
	Amikacin	2 – 32	8	16
	Ethambutol	2 – >32	4	16
	Rifabutin	≤0.03 – 2	0.06	0.25
Mycobacterium avium (n=55)	Epetraborole	0.25 – 16	1	8
	Clarithromycin	0.125 – >32	1	4
	Amikacin	2 – 32	16	16
	Ethambutol	2 – >32	8	16
	Rifabutin	≤0.03 – 0.5	0.06	0.125
Mycobacterium intracellulare (n=55)	Epetraborole	0.25 – 8	2	4
	Clarithromycin	0.125 – >32	1	1
	Amikacin	2 – 16	8	16
	Ethambutol	1 – 16	4	8
	Rifabutin	0.06 – 2	0.125	0.25

RESULTS

Figure 1. Epetraborole MIC Distribution among 110 MAC respiratory isolates from Japanese patients.

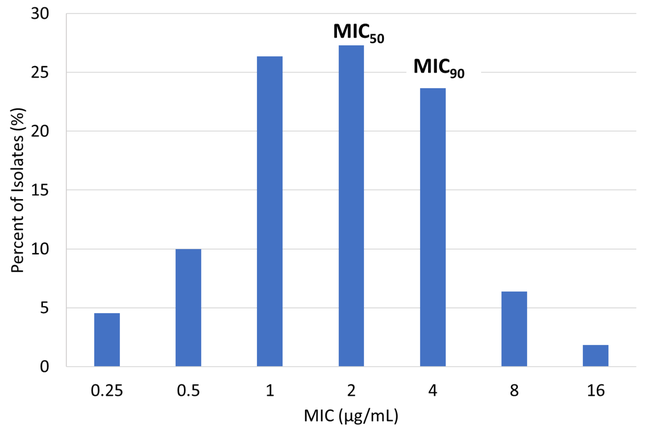

Figure 2. Epetraborole MIC Distribution among *M. avium* and *M. intracellulare* respiratory isolates from Japanese patients.

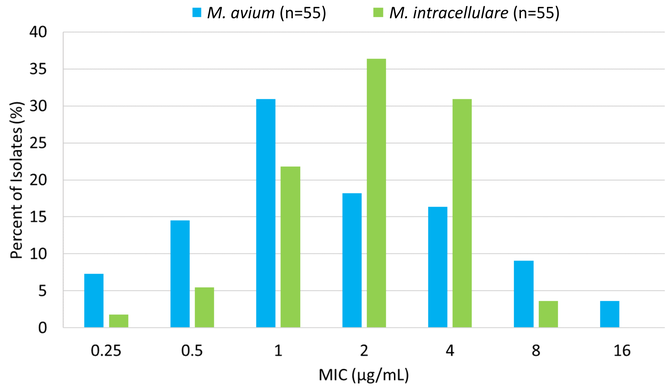

Table 2. Epetraborole and comparator antimicrobial MIC values against clarithromycin-resistant MAC clinical isolates from Japan.

Organism	MIC (µg/mL)				
	Epetraborole	Clarithromycin	Amikacin	Ethambutol	Rifabutin
M. avium MA-026	0.25	>32	8	16	0.06
M. avium MA-028	1	32	16	>32	0.25
M. intracellulare MI-021	2	>32	8	4	2
M. intracellulare MI-037	2	>32	8	2	0.06

CONCLUSIONS

- EBO demonstrated potent *in vitro* activity against 110 recent MAC respiratory isolates collected from Japanese patients
- EBO MIC_{50} = 2 µg/mL and MIC_{90} = 4 µg/mL
- EBO demonstrated *in vitro* activity against CLR-resistant MAC, suggesting that CLR-resistance does not impact EBO activity
- EBO MIC distributions against isolates collected in Japan were similar to EBO MIC distributions against isolates collected from the U.S. isolates
- These data support the continued clinical evaluation of EBO in the treatment of MAC lung disease in Japan.

REFERENCES

[1] Izumi K, Morimoto K, Hasegawa N, Uchimura K, Kawatsu L, Ato M, Mitarai S. *Ann Am Thorac Soc.* 2019 Mar;16(3):341-347.
[2] Furuuchi K, Morimoto K, Yoshiyama T, Tanaka Y, Fujiwara K, Okumura M, Izumi K, Shiraishi Y, Mitarai S, Ogata H, Kurashima A, Yoshimori K, Ohta K, Goto H, Sasaki Y. *Respir Med.* 2019 Jun;152:74-80.
[3] DeStefano, M.S.; Shoen, C.M.; Alley, M.R.K.; Cynamon, M.H. Poster presentation. IDWeek Oct 19-23, 2022, Washington, D.C.

ACKNOWLEDGEMENTS

This study was funded by AN2 Therapeutics (Menlo Park, CA).

Contact: Tiffany Keepers tkeepers@an2therapeutics.com