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In Vitro Activity and Potency of the Novel Oxazolidinone MRX-I Tested against Contemporary Clinical Isolates of Gram-Positive Bacteria

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Abstract

Background: MRX-I is an oral, next generation oxazolidinone antibacterial targeting infections due to multidrug-resistant gram-positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE). Preliminary clinical data suggests that MRX-I is associated with less hematologic toxicity than linezolid in both preclinical models and in Phase 1 and Phase 2 clinical trials. MRX-I is currently in development for the treatment of acute bacterial skin/soft tissue infections.

Methods: A total of 1,211 organisms were randomly selected from bacterial isolates collected in the United States (US; 48 medical centers) and 18 European countries (36 medical centers) in 2015 by the SENTRY Antimicrobial Surveillance Program. The collection included 606 *S. aureus* (34.3% MRSA), 100 coagulase-negative staphylococci (CoNS; 65.0% MR-CoNS), 52 *Enterococcus faecalis*, 51 *E. faecium* (51.0% VRE), 201 *Streptococcus pneumoniae* (SPN), 102 β-haemolytic streptococci (BHS), and 99 viridans group streptococci (VGS).

Results: MRX-I showed potent *in vitro* activity against MRSA and methicillin-susceptible *S. aureus* (MSSA) strains ($MIC_{50/90}$, 0.5/1 µg/mL for both subsets; highest MIC, 2 µg/mL), and it was more potent than linezolid ($MIC_{50/90}$, 1/1 µg/mL). Against CoNS isolates, $MIC_{50/90}$ values for MRX-I and linezolid were 0.25/0.5 µg/mL and 0.5/1 µg/mL, respectively. MRX-I exhibited potent activity against *Enterococcus* spp. isolates, and its *in vitro* activity was very similar to linezolid activity when tested against *E. faecalis* and *E. faecium*, with $MIC_{50/90}$ of 0.5/1 µg/mL for both compounds and both organisms. Further, MRX-I activity was not adversely affected by oxacillin resistance in staphylococci or vancomycin resistance in enterococci. MRX-I was also very active against SPN, BHS, and VGS ($MIC_{50/90}$, 1/1 µg/mL for all three groups; highest MIC, 2 µg/mL), with activity similar to linezolid activity ($MIC_{50/90}$, 1/1 µg/mL for all three groups; highest MIC, 2 µg/mL) against these organisms.

Conclusions: MRX-I was very active against a large collection of contemporary (2015) clinical isolates of gram-positive bacteria from US and European medical centers. *In vitro* activity of MRX-I was comparable to linezolid activity for all organism groups evaluated, and the highest MRX-I MIC value observed was only 2 µg/mL. Results of this investigation support clinical development of MRX-I.

Introduction

- MRX-I is a new ortho-fluoro dihydropyridone oxazolidinone that has shown potent *in vitro* antibacterial activity against resistant gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), penicillin-resistant *Streptococcus pneumoniae* (PRSP), and vancomycin-resistant enterococci (VRE)
- In addition, MRX-I has demonstrated potent *in vivo* efficacy in mouse systemic and local thigh infection models against MRSA, vancomycin-intermediate *S. aureus* (VISA), PRSP, VRE, and high-level gentamicin-resistant enterococci, compared to that of linezolid
- Preliminary clinical data suggests that MRX-I is associated with less hematologic toxicity than linezolid in both preclinical models and in Phase 1 and Phase 2 clinical trials
- MRX-I is currently in development for the treatment of acute bacterial skin and skin structure infections
- We evaluated the *in vitro* antimicrobial activity of MRX-I against contemporary clinical isolates of gram-positive bacteria from United States (US) and European medical centers

Materials and Methods

Susceptibility testing

- MIC values were determined using the reference CLSI broth microdilution method as described in M07-A10
- 96-well frozen-form assay panels were produced by JMI Laboratories (North Liberty, Iowa, USA) and consisted of 2 media types: cation-adjusted Mueller-Hinton broth (CA-MHB) and CA-MHB supplemented with 2.5%-5% lysed horse blood
- MRX-I powder was provided by MicuRx Pharmaceuticals, Inc. (Hayward, California, USA), and comparator agents were provided by JMI Laboratories through Sigma-Aldrich or their respective manufacturer
- Quality control (QC) ranges and interpretive criteria for the comparator compounds were as published in CLSI M100-S27; tested QC strains included *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619

Organism collection

- Organisms were randomly selected from bacterial isolates collected in the US and Europe in 2015 through the SENTRY Antimicrobial Surveillance Program
- The following species/groups were tested (1,211 total):
  - *S. aureus* (606; 398 methicillin-susceptible [MSSA] and 208 MRSA strains)
  - Coagulase-negative staphylococci (100; 35 methicillin-susceptible and 65 methicillin-resistant isolates)
  - *E. faecalis* (52)
  - *E. faecium* (51; 25 vancomycin-susceptible and 26 vancomycin-nonsusceptible [VRE] strains)
  - *Streptococcus pneumoniae* (201)
  - β-haemolytic streptococci (102)
  - Viridans group streptococci (99)

Results

- MRX-I showed potent *in vitro* activity against MRSA and methicillin-susceptible *S. aureus* (MSSA) strains ($MIC_{50/90}$, 0.5/1 µg/mL for both subsets; highest MIC, 2 µg/mL; Table 1 and Figure 1), and it was more potent than linezolid ($MIC_{50/90}$, 1/1 µg/mL; Table 2)
- Vancomycin ($MIC_{50/90}$, 0.5/1 µg/mL; 100.0% susceptible), doxycycline ($MIC_{50/90}$, 0.06/0.12 µg/mL; 99.5% susceptible [CLSI]), and trimethoprim/sulfamethoxazole (TMP-SMX; MIC_{50} and MIC_{90}, ≤0.12 µg/mL; 99.2% susceptible) were also very active against *S. aureus* (Table 2)
- When tested against CoNS isolates, MRX-I ($MIC_{50/90}$, 0.25/0.5 µg/mL) was 2-fold more active than linezolid ($MIC_{50/90}$, 0.5/1 µg/mL; Tables 1 and 2)
- MRX-I exhibited potent activity against *Enterococcus* spp. isolates, and its *in vitro* activity was very similar to linezolid activity when tested against *E. faecalis* and *E. faecium*, with $MIC_{50/90}$ of 0.5/1 µg/mL for both compounds and both organisms (Tables 1 and 2)
- MRX-I activity was not adversely affected by oxacillin resistance in staphylococci or vancomycin resistance in enterococci (Table 1)
- MRX-I was also very active against *S. pneumoniae*, β-haemolytic streptococci, and viridans group streptococci ($MIC_{50/90}$, 1/1 µg/mL for all 3 groups; highest MIC, 2 µg/mL), with activity similar to linezolid activity ($MIC_{50/90}$, 1/1 µg/mL for all 3 groups; highest MIC, 2 µg/mL) against these organisms (Tables 1 and 2)

Table 1 Summary of MRX-I and linezolid activity when tested against 1,211 contemporary gram-positive isolates

	No. of isolates (cumulative %) inhibited at MIC (µg/mL) of:						
Organism	**0.12**	**0.25**	**0.5**	**1**	**2**	**MIC_{50}**	**MIC_{90}**
S. aureus (606)							
MRX-I	2 (0.3)	54 (9.2)	406 (76.2)	142 (99.7)	2 (100.0)	0.5	1
Linezolid	1 (0.2)	10 (1.8)	270 (46.4)	322 (99.5)	3 (100.0)	1	1
MSSA (398)							
MRX-I	2 (0.5)	21 (5.8)	260 (71.1)	113 (99.5)	2 (100.0)	0.5	1
Linezolid	1 (0.3)	4 (1.3)	152 (39.4)	238 (99.2)	3 (100.0)	1	1
MRSA (208)							
MRX-I		33 (15.9)	146 (86.1)	29 (100.0)		0.5	1
Linezolid		6 (2.9)	118 (59.6)	84 (100.0)		0.5	1
CoNS (100)							
MRX-I	12 (12.0)	53 (65.0)	32 (97.0)	3 (100.0)		0.25	0.5
Linezolid	4 (4.0)	39 (43.0)	44 (87.0)	13 (100.0)		0.5	1
E. faecalis (52)							
MRX-I		4 (7.7)	29 (63.5)	15 (92.3)	4 (100.0)	0.5	1
Linezolid		4 (7.7)	27 (59.6)	16 (90.4)	5 (100.0)	0.5	1
E. faecium (51)							
MRX-I		2 (3.9)	30 (62.7)	17 (96.1)	2 (100.0)	0.5	1
Linezolid		2 (3.9)	28 (58.8)	19 (96.1)	2 (100.0)	0.5	1
Vancomycin-susceptible (25)							
MRX-I		1 (4.0)	12 (52.0)	10 (92.0)	2 (100.0)	0.5	1
Linezolid		1 (4.0)	11 (48.0)	11 (92.0)	2 (100.0)	1	1
Vancomycin-nonsusceptible (26)							
MRX-I		1 (3.8)	18 (73.1)	7 (100.0)		0.5	1
Linezolid		1 (3.8)	17 (69.2)	8 (100.0)		0.5	1
S. pneumoniae (201)							
MRX-I		2 (1.0)	35 (18.4)	160 (98.0)	4 (100.0)	1	1
Linezolid		2 (1.0)	34 (17.9)	161 (98.0)	4 (100.0)	1	1
β-haemolytic streptococci (102)							
MRX-I			4 (3.9)	95 (97.1)	3 (100.0)	1	1
Linezolid			3 (2.9)	97 (98.0)	2 (100.0)	1	1
Viridans group streptococci (99)							
MRX-I	1 (1.0)	4 (5.1)	29 (34.3)	64 (99.0)	1 (100.0)	1	1
Linezolid		5 (5.1)	28 (33.3)	65 (99.0)	1 (100.0)	1	1

Figure 1 Antimicrobial activity of MRX-I and linezolid when tested against 606 *S. aureus* clinical isolates

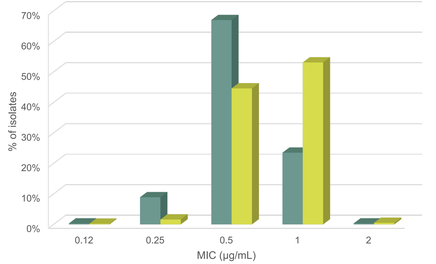

Table 2 Activity of MRX-I and comparator antimicrobial agents when tested against gram-positive organisms from US and European medical centers

Organism/antimicrobial agent			CLSI[a]		EUCAST[a]	
(no. tested)	**MIC_{50}**	**MIC_{90}**	**%S**	**%R**	**%S**	**%R**
S. aureus (606)						
MRX-I	0.5	1	—	—	—	—
Linezolid	1	1	100.0	0.0	100.0	0.0
Oxacillin	0.5	>4	65.7	34.3	65.7	34.3
Doxycycline	0.06	0.12	99.2	0.3	97.2	2.1
Erythromycin	0.5	>8	50.3	45.9	52.5	47.4
Clindamycin	≤0.06	>4	87.0	12.9	86.8	13.0
Levofloxacin	0.25	>8	69.1	30.9	69.1	30.9
TMP-SMX	≤0.12	≤0.12	99.2	0.8	99.2	0.5
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
MRSA (208)						
MRX-I	0.5	1	—	—	—	—
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Doxycycline	0.06	0.25	98.6	0.5	96.2	2.9
Erythromycin	>8	>8	11.1	87.5	11.5	88.5
Clindamycin	≤0.06	>4	66.8	33.2	66.8	33.2
Levofloxacin	8	>8	20.7	79.3	20.7	79.3
TMP-SMX	≤0.12	≤0.12	98.1	1.9	98.1	1.0
Vancomycin	0.5	1	100.0	0.0	100.0	0.0
CoNS (100)						
MRX-I	0.25	0.5	—	—	—	—
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Oxacillin	4	>4	35.0	65.0	35.0	65.0
Doxycycline	0.12	0.5	100.0	0.0	96.0	1.0
Erythromycin	>8	>8	43.0	56.0	44.0	56.0
Clindamycin	≤0.06	>4	71.0	27.0	70.0	29.0
Levofloxacin	0.5	>8	54.0	40.0	54.0	40.0
TMP-SMX	≤0.12	>4	69.0	31.0	69.0	18.0
Vancomycin	1	2	100.0	0.0	100.0	0.0
E. faecalis (52)						
MRX-I	0.5	1	—	—	—	—
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Levofloxacin	1	>8	75.0	25.0	75.0	25.0[b]
Vancomycin	1	2	98.1	1.9	98.1	1.9
E. faecium (51)						
MRX-I	0.5	1	—	—	—	—
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Levofloxacin	>8	>8	5.9	92.2	7.8	92.2[b]
Vancomycin	>16	>16	49.0	51.0	49.0	51.0
Vancomycin-nonsusceptible (26)						
MRX-I	0.5	1	—	—	—	—
Linezolid	0.5	1	100.0	0.0	100.0	0.0
Levofloxacin	>8	>8	0.0	100.0	0.0	100.0[b]
Vancomycin	>16	>16	0.0	100.0	0.0	100.0
S. pneumoniae (201)						
MRX-I	1	1	—	—	—	—
Linezolid	1	1	100.0	—	100.0	0.0
Ceftriaxone	0.03	1	90.0	2.5[b]	90.0	0.5
Erythromycin	0.12	>8	97.5	0.5[c]	—	—
Doxycycline	0.12	8	66.2	33.3	66.2	33.3
Clindamycin	≤0.06	>4	76.1	23.4	77.1	22.4
Levofloxacin	1	1	83.1	16.4	83.6	16.4
TMP-SMX	0.25	>4	100.0	0.0	100.0	0.0
Vancomycin	0.25	0.25	69.2	16.4	75.6	16.4
β-haemolytic streptococci (102)			100.0	—	100.0	0.0
MRX-I	1	1	—	—	—	—
Linezolid	1	1	100.0	—	100.0	0.0
Ceftriaxone	0.03	0.06	100.0	—	100.0	0.0
Erythromycin	0.12	>8	72.5	27.5	72.5	27.5
Doxycycline	0.12	16	—	—	57.8	42.2
Clindamycin	≤0.06	>4	82.4	17.6	82.4	17.6
Levofloxacin	0.5	2	98.0	0.0	88.2	2.0
TMP-SMX	≤0.12	≤0.12	—	—	99.0	1.0
Vancomycin	0.25	0.5	100.0	—	100.0	0.0
Viridans group streptococci (9)						
MRX-I	1	1	—	—	—	—
Linezolid	1	1	100.0	—	—	—
Ceftriaxone	0.12	0.5	94.9	4.0	93.9	6.1
Erythromycin	2	>8	47.5	52.5	—	—
Clindamycin	≤0.06	>4	84.8	13.1	86.9	13.1
Levofloxacin	1	2	93.9	4.0	—	—
Vancomycin	0.5	0.5	100.0	—	100.0	0.0

a. Criteria as published by CLSI (2017) and EUCAST (2017). "—" indicates that no breakpoint has been established.
Abbreviations: TMP-SMX, trimethoprim-sulfamethoxazole

Conclusions

- MRX-I was very active against a large collection of contemporary (2015) gram-positive bacteria clinical isolates from US and European medical centers
- MRX-I *in vitro* activity was comparable to linezolid activity for all organism groups evaluated, and the highest MRX-I MIC value observed was only 2 µg/mL
- Results of this investigation support clinical development of MRX-I

Acknowledgements

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