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In vitro Evaluation of Delafloxacin Activity When Tested against Contemporary Multidrug-Resistant *Streptococcus pneumoniae* (2014–2017): Results from the SENTRY Antimicrobial Surveillance Program

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Abstract

Background: Delafloxacin is a broad-spectrum fluoroquinolone (FQ) antibacterial that was approved in 2017 by the Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). Delafloxacin is also in clinical development for community-acquired bacterial pneumonia (CABP). In this study, *in vitro* susceptibility (S) results for delafloxacin and comparator agents were determined for *Streptococcus pneumoniae* (SPN) clinical isolates from US and European hospitals participating in the SENTRY Surveillance Program during 2014–2017.

Methods: A total of 3,629 SPN isolates were collected during 2014–2017 from US and European hospitals and included only 1 isolate/patient/infection episode. Isolate identifications were confirmed at JMI Laboratories. Susceptibility testing was performed according to CLSI broth microdilution methodology, and outcomes were interpreted per CLSI (2017) breakpoints where applicable. Other antimicrobials tested included levofloxacin (LVX) and moxifloxacin (MOX). Multidrug-resistant (MDR) isolates were categorized as being nonsusceptible (NS) to amoxicillin-clavulanate, erythromycin, and tetracycline. Fluoroquinolone-resistant (FQR) isolates were NS to LVX (MIC ≥4 mg/L).

Results: The 3 most common infection types were community-acquired respiratory tract infection (n=2,845), bloodstream infection (n=369), and pneumonia in hospitalized patients (n=285). Delafloxacin demonstrated potent *in vitro* activity against SPN ($MIC_{50/90}$ 0.015/0.03 mg/L) and was more active than LVX ($MIC_{50/90}$ 1/1 mg/L) or MOX ($MIC_{50/90}$ ≤0.12/0.25 mg/L). Delafloxacin was also more active against 155 MDR SPN isolates ($MIC_{50/90}$ 0.03/0.03 mg/L) than LVX ($MIC_{50/90}$ 1/2 mg/L) or MOX ($MIC_{50/90}$ ≤0.12/0.25 mg/L). For 58 FQR SPN, the delafloxacin $MIC_{50/90}$ values were 0.12/0.25 mg/L with all but 3 isolates having delafloxacin MIC values ≤0.25 mg/L.

Conclusions: Delafloxacin demonstrated extremely potent *in vitro* antibacterial activity against SPN, including MDR isolates that were NS to the antimicrobials most commonly used as treatments for CABP. Delafloxacin was the most potent FQ and had excellent activity against LVX-NS SPN. These data support the continued study of delafloxacin as a potential treatment for SPN infections, including CABP.

Introduction

- Delafloxacin is a broad-spectrum fluoroquinolone (FQ) antibacterial that was approved in 2017 by the United States Food and Drug Administration for the treatment of acute bacterial skin and skin structure infections (ABSSSIs)
- Delafloxacin is also in clinical development for community-acquired bacterial pneumonia (CABP)
- In this study, the *in vitro* susceptibility (S) for delafloxacin and comparator agents was determined for *Streptococcus pneumoniae* clinical isolates from US and European hospitals participating in the SENTRY Surveillance Program during 2014–2017

Materials and Methods

- A total of 3,629 *S. pneumoniae* isolates were collected during 2014–2017 from US and European hospitals
  - Only 1 isolate/patient/infection episode was included
  - Isolate identifications were confirmed at JMI Laboratories
- Susceptibility testing of delafloxacin was performed according to CLSI broth microdilution methodology and interpreted per CLSI (2018) breakpoints, where applicable
- Other antimicrobials tested included levofloxacin, moxifloxacin, penicillin, amoxicillin-clavulanic acid, ceftriaxone, erythromycin, clindamycin, tetracycline, and trimethoprim-sulfamethoxazole
- Multidrug-resistant (MDR) isolates were categorized using CLSI criteria as being nonsusceptible (NS) to amoxicillin-clavulanate, erythromycin, and tetracycline
- Levofloxacin-NS (MIC ≥4 mg/L) and moxifloxacin-NS (MIC ≥2 mg/L) phenotypes were also analyzed

Results

- The 3 most common infection types were community-acquired respiratory tract infection (n=2,845), bloodstream infection (n=369), and pneumonia in hospitalized patients (n=285)
- Delafloxacin demonstrated potent *in vitro* activity against *S. pneumoniae* ($MIC_{50/90}$ 0.015/0.03 mg/L) and was 32X-64X more active than levofloxacin ($MIC_{50/90}$ 1/1 mg/L) and 8X more active than moxifloxacin ($MIC_{50/90}$ ≤0.12/0.25 mg/L), as shown in Table 1 and Figure 1
- MIC distributions of US and European isolates for the 3 fluoroquinolones tested were very similar (Figure 1)
- Delafloxacin was more active against 155 MDR *S. pneumoniae* isolates ($MIC_{50/90}$ 0.03/0.03 mg/L) than levofloxacin ($MIC_{50/90}$ 1/2 mg/L) or moxifloxacin ($MIC_{50/90}$ ≤0.12/0.25 mg/L); see Table 1
- MIC distributions of delafloxacin for all isolates, MDR isolates, and levofloxacin-NS isolates are shown in Table 2
  - All MDR isolates had delafloxacin MIC values ≤0.12 mg/L
- For 58 levofloxacin-NS *S. pneumoniae* isolates, the delafloxacin $MIC_{50/90}$ values were 0.12/0.25 mg/L (Figure 2)
  - 94.8% of isolates had delafloxacin MIC values ≤0.25 mg/L
- For 40 moxifloxacin-NS isolates, the delafloxacin $MIC_{50/90}$ values were 0.12/0.25 mg/L (Figure 2)
  - 92.5% of isolates had delafloxacin $MIC_{50/90}$ values ≤0.25 mg/L

Figure 1 Comparison of activities of delafloxacin (DLX), levofloxacin (LVX), and moxifloxacin (MOX) tested against 1,825 US and 1,804 European *S. pneumoniae* isolates

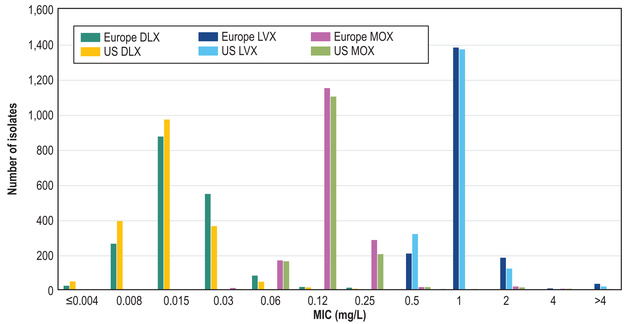

Figure 2 Activity of delafloxacin against 58 levofloxacin nonsusceptible (LVX-NS) and 40 moxifloxacin nonsusceptible (MOX-NS) *S. pneumoniae* isolates

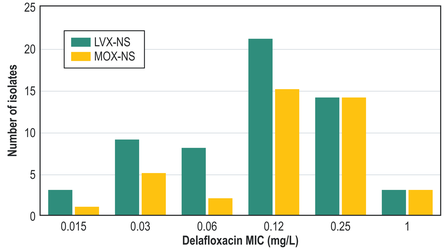

Table 1 Activity of delafloxacin and comparators when tested against *Streptococcus pneumoniae*, including MDR and levofloxacin-NS isolates

Antimicrobial agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC range (mg/L)	CLSI[a] %S	CLSI[a] %I	CLSI[a] %R	EUCAST[a] %S	EUCAST[a] %I	EUCAST[a] %R
All (n=3,629)									
Delafloxacin	0.015	0.03	≤0.004 — 1						
Levofloxacin	1	1	≤0.06 — >4	98.4	0.2	1.4	98.4		1.6
Moxifloxacin	≤0.12	0.25	≤0.12 — >4	98.7	0.9	0.4	98.6		1.4
Amoxicillin-clavulanate (2:1)	≤1	2	≤1 — >4	94.3	2.5	3.3			
Ceftaroline	≤0.015	0.12	≤0.015 — 1	99.9		[b]	99.7		0.3
Ceftriaxone	≤0.06	1	≤0.06 — >2	87.3	9.3	3.4[c]	87.3	12.0	0.7
				96.6	2.7	0.7[b]			
Clindamycin	≤0.25	>1	≤0.25 — >1	83.8	0.4	15.7	84.3		15.7
Erythromycin	≤0.12	>2	≤0.12 — >2	65.0	0.6	34.4	65.0	0.6	34.4
Linezolid	1	2	≤0.12 — 2	100.0			100.0	0.0	0.0
Meropenem	≤0.015	0.5	≤0.015 — >1	84.7	9.5	5.8	84.7	15.1	0.2[c]
							100.0		0.0[b]
Penicillin	≤0.06	2	≤0.06 — >4	67.9	21.3	10.9[d]	67.9		32.1[e]
				67.9		32.1[e]	67.9	27.7	4.4[b]
				95.6	4.2	0.3[f]			
Tetracycline	≤0.5	>4	≤0.5 — >4	78.4	0.3	21.3	78.4	0.3	21.3
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 — >4	73.3	9.8	16.8	78.9	4.2	16.8
MDR (n=155)									
Delafloxacin	0.03	0.03	0.008 — 0.12						
Levofloxacin	1	2	0.5 — >4	97.4	0.6	1.9	97.4		2.6
Moxifloxacin	≤0.12	0.25	≤0.12 — 4	99.3	0.0	0.7	99.3		0.7
Amoxicillin-clavulanate (2:1)	>4	>4	4 — >4	0.0	45.8	54.2			
Ceftaroline	0.12	0.25	0.06 — 1	99.4		[b]	95.5		4.5
Ceftriaxone	2	>2	0.5 — >2	3.2	42.6	54.2[c]	3.2	85.2	11.6
				45.8	42.6	11.6[b]			
Clindamycin	>1	>1	≤0.25 — >1	16.1	1.9	81.9	18.1		81.9
Erythromycin	>2	>2	0.5 — >2	0.0	0.6	99.4	0.0	0.6	99.4
Linezolid	1	1	0.25 — 2	100.0			100.0	0.0	0.0
Meropenem	1	1	0.5 — >1	0.0	21.0	79.0	0.0	97.8	2.2[c]
							100.0		0.0[b]
Penicillin	4	4	1 — >4	0.0	1.3	98.7[d]	0.0		100.0[e]
				0.0		100.0[e]	0.0	23.9	76.1[b]
				23.9	70.3	5.8[f]			
Tetracycline	>4	>4	>4 — >4	0.0	0.0	100.0	0.0	0.0	100.0
Trimethoprim-sulfamethoxazole	>4	>4	≤0.5 — >4	6.5	3.2	90.3	8.4	1.3	90.3
Levofloxacin-nonsusceptible (n=58)									
Delafloxacin	0.12	0.25	0.015 — 1						
Levofloxacin	>4	>4	4 — >4	0.0	15.5	84.5	0.0		100.0
Moxifloxacin	2	4	0.12 — >4	32.1	49.1	18.9	28.3		71.7
Amoxicillin-clavulanate (2:1)	≤1	4	≤1 — >4	89.7	3.4	6.9			
Ceftaroline	≤0.015	0.12	≤0.015 — 0.25	100.0		[b]	100.0		0.0
Ceftriaxone	≤0.06	1	≤0.06 — >2	82.8	8.6	8.6[c]	82.8	13.8	3.4
				91.4	5.2	3.4[b]			
Clindamycin	≤0.25	>1	≤0.25 — >1	74.1	0.0	25.9	74.1		25.9
Erythromycin	≤0.12	>2	≤0.12 — >2	60.3	1.7	37.9	60.3	1.7	37.9
Linezolid	1	2	0.5 — 2	100.0			100.0	0.0	0.0
Meropenem	≤0.015	0.5	≤0.015 — 1	81.1	9.4	9.4	81.1	18.9	0.0[c]
							100.0		0.0[b]
Penicillin	≤0.06	2	≤0.06 — 4	60.3	22.4	17.2[d]	60.3		39.7[e]
				60.3		39.7[e]	60.3	32.8	6.9[b]
				93.1	6.9	0.0[f]			
Tetracycline	≤0.5	>4	≤0.5 — >4	63.8	0.0	36.2	63.8	0.0	36.2
Trimethoprim-sulfamethoxazole	≤0.5	>4	≤0.5 — >4	62.1	5.2	32.8	62.1	5.2	32.8

MDR, multidrug-resistant; nonsusceptible (NS) to amoxicillin-clavulanate, erythromycin, and tetracycline; susceptible (S); intermediate (I); resistant (R)
[a] Criteria as published by CLSI 2018 and EUCAST 2018.
[b] Using nonmeningitis breakpoints.
[c] Using meningitis breakpoints.
[d] Using oral breakpoints.
[e] Using parenteral, meningitis breakpoints.
[f] Using parenteral, nonmeningitis breakpoints.

Table 2 Antimicrobial activity of delafloxacin tested against the main organisms and organism groups of isolates

Organism/organism group (no. of isolates)	No. of isolates at MIC (mg/L; cumulative %) ≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	>	MIC_{50}	MIC_{90}
Streptococcus pneumoniae (3,629)	67 1.8	651 19.8	1,839 70.5	905 95.4	123 98.8	27 99.5	14 99.9	0 99.9	3 100.0		0.015	0.03
MDR *Streptococcus pneumoniae* (155)	0 0.0	23 14.8	53 49.0	64 90.3	12 98.1	3 100.0					0.03	0.03
Levofloxacin-nonsusceptible (MIC >2 mg/L) (58)		0 0.0	3 5.2	9 20.7	8 34.5	21 70.7	14 94.8	0 94.8	3 100.0		0.12	0.25
Moxifloxacin-nonsusceptible (MIC >1 mg/L) (40)		0 0.0	1 3.0	5 15.0	2 20.0	15 57.5	14 92.5	0 92.5	3 100.0		0.12	0.25

MDR, multidrug-resistant

Conclusions

- Delafloxacin demonstrated extremely potent *in vitro* antibacterial activity against *S. pneumoniae*, including MDR isolates that were NS to the antimicrobials most commonly used as treatments for community-acquired bacterial pneumonia, amoxicillin-clavulanate, erythromycin, and tetracycline
  - 100% of MDR *S. pneumoniae* isolates were inhibited by ≤0.12 mg/L of delafloxacin
- Delafloxacin was the most potent fluoroquinolone tested and had excellent activity against levofloxacin-NS and moxifloxacin-NS *S. pneumoniae* isolates
  - 92.5% of fluoroquinolone-NS isolates were inhibited by a delafloxacin concentration ≤0.25 mg/L
- These data support the continued study of delafloxacin as a potential treatment for *S. pneumoniae* infections, including community-acquired bacterial pneumonia

Acknowledgements

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