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In Vitro Activity of Lefamulin (LEF) Against Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CABP): 2016 SENTRY Data From the United States

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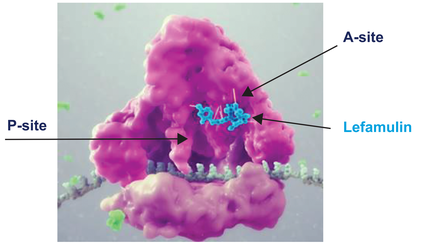
INTRODUCTION

- Pneumonia is a major cause of morbidity and mortality in adults and children around the world[1]
- The most commonly isolated bacterial pathogen from community-acquired bacterial pneumonia (CABP) is *Streptococcus pneumoniae*, with varying rates depending on geographic region; other causes of CABP include *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, as well as atypical pathogens such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydophila pneumoniae*[2-8]
- Antibiotic resistance rates are rising, and there is a need for new therapies to treat CABP
  - Each year in the United States (US), ≥2 million people develop bacterial infections that are resistant to antibiotics, directly resulting in ≥23,000 deaths[9]
  - Drug-resistant *S. pneumoniae* and methicillin-resistant *S. aureus* (MRSA) have reached the serious threat level in the US, requiring prompt and sustained action to ensure the problem does not grow[10]
- The Centers for Disease Control and Prevention Antibiotic Resistance Solutions Initiative is providing extramural funding to detect, respond, and contain resistant pathogens; prevent the spread of resistant infections; and encourage innovation for new strategies, drugs, and diagnostics[11]
- Lefamulin, a semisynthetic pleuromutilin antibiotic in late-stage clinical development for the treatment of CABP, inhibits protein synthesis in CABP pathogens by a unique mechanism of action **(Figure 1)**[12,13]
  - Lefamulin interacts with the peptidyl transferase center (PTC) via 4 hydrogen bonds; the pleuromutilin core binds to the A-site while the C14 side chain binds to the P-site within domain V of 23S rRNA
  - Binding of the C14 extension in the P-site results in the bonded nucleotide translating away from the extension while another rotates toward the binding pocket, thus tightening the binding pocket around the mutilin core in the A-site and creating an induced fit
  - This induced fit mechanism inhibits the correct positioning of the CCA ends of the tRNA and hinders peptide transfer during A- to P-site rotary motion, ultimately inhibiting peptide bond formation
- The objective of this analysis was to investigate the *in vitro* activity of lefamulin and comparators against a contemporary set of pathogens collected in the US that commonly cause CABP

Figure 1. Lefamulin in the Peptidyl Transferase Center (PTC)



PTC of the 23S rRNA of the large ribosomal subunit

METHODS

- 1926 isolates were collected from 32 medical centers in the US as part of the SENTRY Surveillance Program, including *S. pneumoniae* (*n*=815), *S. aureus* (*n*=550), *H. influenzae* (*n*=223), and *M. catarrhalis* (*n*=86)
- Lefamulin and comparators were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods, and susceptibility was determined using CLSI (2018) breakpoints

RESULTS

S. pneumoniae

- Lefamulin demonstrated potent *in vitro* activity against *S. pneumoniae* with $MIC_{50/90}$ of 0.12/0.12 µg/mL (range, 0.015–1 µg/mL; **Table 1**) and 99.8% of all isolates inhibited at MIC ≤0.5 µg/mL
- Penicillin-susceptible (*n*=790; MIC ≤2 µg/mL) and penicillin-nonsusceptible (*n*=25; MIC >2 µg/mL) *S. pneumoniae* isolates maintained similar lefamulin $MIC_{50/90}$ values (0.12/0.12 µg/mL and 0.06/0.12 µg/mL, respectively)
- *S. pneumoniae* isolates were susceptible (>80%) to most comparators, but resistance rates of >20% were reported for azithromycin and erythromycin **(Table 1)**

S. aureus

- Lefamulin was active against *S. aureus* ($MIC_{50/90}$ of 0.06/0.12 µg/mL; **Table 1**) with 99.5% of all isolates and 99.1% of MRSA being inhibited at MIC ≤0.25 µg/mL
- *S. aureus* isolates were susceptible (>80%) to most comparators, but resistance rates of >20% were reported for azithromycin, erythromycin, levofloxacin, moxifloxacin, and oxacillin **(Table 1)**
- The 42.4% of *S. aureus* isolates identified as MRSA showed particularly high resistance rates to oxacillin (100%), azithromycin (89.7%), erythromycin (87.1%), levofloxacin (71.2%), moxifloxacin (44.6%), and clindamycin (33.5%; **Table 1**)

H. influenzae

- Lefamulin demonstrated activity against *H. influenzae* ($MIC_{50/90}$ of 0.5/1 µg/mL; **Table 2**) with 99.6% of all isolates and 100% of β-lactamase–positive strains inhibited at MIC ≤2 µg/mL
- *H. influenzae* isolates were susceptible (>80%) to most comparators, but resistance rates of >20% were reported for ampicillin and trimethoprim-sulfamethoxazole **(Table 2)**

M. catarrhalis

- 100% of *M. catarrhalis* isolates were inhibited at lefamulin concentrations ≤0.12 µg/mL ($MIC_{50/90}$ of 0.06/0.06 µg/mL; **Table 2**)
- *M. catarrhalis* isolates were susceptible (97.7%–100%) to all comparators **(Table 2)**
- Nearly all *M. catarrhalis* isolates (96.8%) tested positive for β-lactamase

RESULTS (continued)

Table 1. Activity of Lefamulin and Comparators Against Gram-Positive Pathogens Commonly Causing CABP

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Streptococcus pneumoniae* (*n*=815)**						
Lefamulin	0.12	0.12	0.015–1	NA	NA	NA
Amoxicillin-clavulanic acid	≤0.03	2	≤0.03–>4	94.9	3.3	1.7
Azithromycin	0.12	>32	0.015–>32	54.2	1.2	44.5
Ceftaroline	≤0.008	0.12	≤0.008–0.5	100.0		
Ceftriaxone	0.03	1	≤0.015–>2	85.7 97.7	11.9 1.8	2.3[b] 0.5[c]
Clindamycin	≤0.25	>2	≤0.25–>2	85.3	0.4	14.4
Erythromycin	0.06	>32	≤0.015–>32	53.9	0.7	45.4
Levofloxacin	1	1	0.25–>4	99.1	0.1	0.7
Moxifloxacin	0.12	0.25	≤0.03–>4	99.3	0.4	0.4
Penicillin	0.015	2	≤0.004–8	63.9 63.9 96.9	23.8 2.9	12.3[d] 36.1[e] 0.1[f]
Tetracycline	≤0.25	>8	≤0.25–>8	80.4	0.6	19.0
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12–>4	72.4	10.5	17.1
***Staphylococcus aureus* (*n*=550)**						
Lefamulin	0.06	0.12	≤0.008–2	NA	NA	NA
Azithromycin	32	>32	0.12–>32	42.7	0.7	56.5
Ceftaroline	0.25	1	≤0.06–2	98.2	1.8	0.0
Clindamycin	≤0.25	>2	≤0.25–>2	82.7	0.4	16.9
Doxycycline	≤0.06	0.25	≤0.06–8	99.3	0.7	0.0
Erythromycin	8	>8	≤0.06–>8	42.2	7.1	50.7
Gentamicin	≤1	≤1	≤1–>8	97.6	0.4	2.0
Levofloxacin	0.25	>4	0.06–>4	60.5	2.5	36.9
Linezolid	1	1	0.25–2	100.0		0.0
Moxifloxacin	≤0.06	>4	≤0.06–>4	61.3	16.4	22.4
Oxacillin	0.5	>2	≤0.25–>2	57.6		42.4
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	97.3		2.7
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0
MRSA (*n*=233)						
Lefamulin	0.06	0.12	0.015–2	NA	NA	NA
Azithromycin	>32	>32	0.25–>32	10.3	0.0	89.7
Ceftaroline	0.5	1	0.25–2	95.7	4.3	0.0
Clindamycin	≤0.25	>2	≤0.25–>2	66.5	0.0	33.5
Doxycycline	≤0.06	0.5	≤0.06–8	98.3	1.7	0.0
Erythromycin	>8	>8	≤0.06–>8	9.9	3.0	87.1
Gentamicin	≤1	≤1	≤1–>8	94.8	0.9	4.3
Levofloxacin	4	>4	0.12–>4	23.6	5.2	71.2
Linezolid	0.5	1	0.25–2	100.0		0.0
Moxifloxacin	1	>4	≤0.06–>4	24.9	30.5	44.6
Oxacillin	>2	>2	>2–>2	0.0		100.0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	94.4		5.6
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0

CABP=community-acquired bacterial pneumonia; CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; MRSA=methicillin-resistant *S. aureus*; NA=not applicable; R=resistant; S=susceptible.

[a]Criteria as published by CLSI (2018). [b]Using meningitis breakpoints. [c]Using nonmeningitis breakpoints. [d]Using oral breakpoints. [e]Using parenteral, meningitis breakpoints. [f]Using parenteral, nonmeningitis breakpoints.

RESULTS (continued)

Table 2. Activity of Lefamulin and Comparators Against Gram-Negative Pathogens Commonly Causing CABP

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Haemophilus influenzae* (*n*=223)**						
Lefamulin	0.5	1	0.06–4	NA	NA	NA
Amoxicillin-clavulanic acid	1	2	0.12–8	99.1		0.9
Ampicillin	1	>8	0.12–>8	62.8	8.5	28.7
Azithromycin	1	1	0.12–4	100.0		
Cefepime	0.06	0.25	≤0.015–1	100.0		
Ceftriaxone	0.004	0.015	≤0.001–0.25	100.0		
Ciprofloxacin	0.015	0.015	0.004–>1	99.6		
Clarithromycin	8	8	1–>16	92.8	5.8	1.3
Moxifloxacin	0.03	0.06	0.008–1	100.0		
Tetracycline	0.5	1	0.25–>8	99.6	0.0	0.4
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06–>4	63.7	2.2	34.1
***Moraxella catarrhalis* (*n*=86)**						
Lefamulin	0.06	0.06	≤0.008–0.12	NA	NA	NA
Amoxicillin-clavulanic acid	0.12	0.25	≤0.06–0.5	100.0		0.0
Azithromycin	0.015	0.03	0.008–0.03	100.0		
Ceftriaxone	0.25	1	0.008–2	100.0		
Clarithromycin	≤0.12	0.25	≤0.12–0.25	100.0		
Erythromycin	0.12	0.25	≤0.015–0.25	100.0		
Moxifloxacin	0.06	0.06	0.03–0.12			
Tetracycline	0.25	0.5	0.12–0.5	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	0.12	0.25	≤0.06–1	97.7	2.3	0.0

CABP=community-acquired bacterial pneumonia; CLSI=Clinical and Laboratory Standards Institute; I=intermediate; MIC_{50}=minimum concentration at which 50% of the isolates were inhibited; MIC_{90}=minimum concentration at which 90% of the isolates were inhibited; NA=not applicable; R=resistant; S=susceptible.

[a]Criteria as published by CLSI (2018).

CONCLUSIONS

- Testing of bacterial isolates from the 2016 SENTRY Surveillance Program showed that for pathogens collected in the US commonly causing CABP, significant proportions of isolates were resistant to antibiotics commonly used to treat CABP
- Lefamulin demonstrated potent *in vitro* activity against *S. pneumoniae*, *S. aureus* (including MRSA), *H. influenzae*, and *M. catarrhalis*
- The activity of lefamulin was unaffected by resistance to other antibiotic classes, including macrolides, lincosamides, β-lactams, fluoroquinolones, and tetracyclines
- In light of the current healthcare crisis resulting from the continued development of antibacterial resistance, these data support the ongoing clinical development of lefamulin for the treatment of CABP and other respiratory tract infections

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Disclosures

Susanne Paukner and Steven P. Gelone are employees of Nabriva Therapeutics. Robert K. Flamm and Helio S. Sader are employees of JMI Laboratories, which was contracted by Nabriva to conduct the susceptibility testing.

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