1365

In Vitro Activity of Lefamulin (LEF) Against Bacterial Pathogens Causing Community-Acquired Bacterial Pneumonia (CABP): SENTRY Surveillance 2016 Results From Asia-Pacific (APAC) and Latin America (LA)

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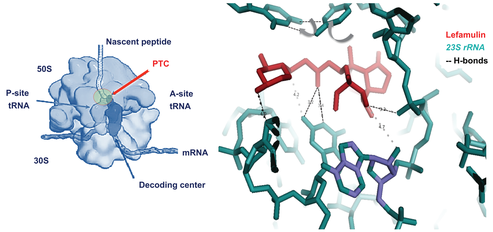
INTRODUCTION

- Pneumonia is a major cause of morbidity and mortality in adults and children around the world,[1] with an estimated 1 million adult deaths per year in Asia. In Latin America (LA), high incidences of community-acquired bacterial pneumonia (CABP) and high mortality rates have been reported that exceed those reported for Europe or the United States[2,3]
- The etiology of pneumonia in Asia and LA is similar to that reported in the West, though Gram-negative bacteria such as *Klebsiella pneumoniae* and *Mycobacterium tuberculosis* play a more important role in Asia.[4] Still, *Streptococcus pneumoniae* remains the most commonly isolated bacterial pathogen from CABP; other bacterial causes of CABP include *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus* as well as atypical pathogens, such as *Legionella pneumophila*, *Mycoplasma pneumoniae*, and *Chlamydia pneumoniae*[5-11]
- Although there are variations by major geographic regions, antibacterial resistance rates are rising in many Asia-Pacific (APAC) and LA countries, complicating treatment, increasing the severity of the disease, and often prolonging hospital stays[3,12]
- Lefamulin, a semisynthetic pleuromutilin antibiotic in clinical development for the treatment of CABP, has a unique mechanism of action
  - Lefamulin inhibits protein synthesis in CABP pathogens by binding to the A- and P-sites in the peptidyl transferase center of the 50S ribosomal subunit via an "induced fit" mechanism[3,14] **(Figure 1)**
- The objective of this analysis was to investigate the *in vitro* activity of lefamulin and comparators against a set of pathogens collected in the APAC region and LA that commonly cause CABP

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



METHODS

- Unique isolates (total *n*=1019) of *S. pneumoniae*, *S. aureus*, *H. influenzae*, and *M. catarrhalis* were collected from patients with pneumonia/respiratory (*n*=551), blood stream (*n*=169), skin and soft tissue (*n*=244), and other (*n*=55) infections
  - 6 countries (Argentina, Australia, Brazil, Chile, Mexico, New Zealand) in APAC (*n*=587)
  - 5 countries (Korea, Malaysia, Singapore, Taiwan, Thailand) in LA (*n*=432)
- Lefamulin and comparators were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods, and susceptibility was determined using CLSI (2018) breakpoints

RESULTS

- In both APAC and LA, lefamulin showed potent *in vitro* activity against this recent collection of respiratory pathogens

S. pneumoniae

- Lefamulin was highly active against *S. pneumoniae* in APAC and LA (minimum inhibitory concentration required to inhibit 50% [MIC_{50}] and 90% [MIC_{90}] of isolates of 0.06 and 0.12 µg/mL, respectively; range 0.015–0.25 µg/mL; **Table 1**) with 100% of all isolates from both APAC and LA being inhibited at MIC ≤0.25 µg/mL
  - Penicillin-resistant *S. pneumoniae* isolates maintained the same lefamulin $MIC_{50/90}$ values (0.06/0.12 µg/mL)
- *S. pneumoniae* isolates were susceptible (>80%) to most comparators, but resistance rates >20% were reported for azithromycin, clindamycin, erythromycin, penicillin (oral and parentheral, meningitis breakpoints), tetracycline, and trimethoprim-sulfamethoxazole **(Table 1)**
  - Resistance rates were particularly high for the penicillin-resistant isolates (93.2% for erythromycin, 88.2% for azithromycin, 85.5% for tetracycline, 73.0% for clindamycin, and 67.1% for trimethoprim-sulfamethoxazole when using CLSI oral breakpoints)

S. aureus

- Lefamulin was active against *S. aureus* in APAC and LA ($MIC_{50/90}$ of 0.06/0.06 µg/mL; range, ≤0.008–16 µg/mL; **Table 1**) with 99.6% of all isolates from both APAC and LA being inhibited at MIC ≤0.25 µg/mL
- *S. aureus* isolates were susceptible (>80%) to most comparators, but resistance rates >20% were reported for azithromycin, erythromycin, and oxacillin **(Table 1)**
- Lefamulin was highly active against methicillin-resistant *S. aureus* (MRSA; MIC_{50} and MIC_{90} of isolates were 0.06 and 0.12 µg/mL, respectively; range, 0.015–0.25 µg/mL) with 100% of these pathogens being inhibited at MIC ≤0.25 µg/mL
  - MRSA isolates were largely susceptible to ceftaroline, doxycycline, linezolid, and vancomycin, but resistance rates >50% were reported for oxacillin (100%), azithromycin (63.5%), levofloxacin (62.2%), erythromycin (61.5%), and moxifloxacin (51.4%; **Table 1**)

RESULTS (continued)

Table 1. Activity of Lefamulin and Comparators Against Gram-Positive Pathogens Commonly Causing CABP (APAC and LA Combined)

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Streptococcus pneumoniae* (*n*=320)**						
Lefamulin	0.06	0.12	0.015–0.25	NA	NA	NA
Amoxicillin-clavulanic acid	≤0.03	4	≤0.03–>4	85.9	4.9	9.2
Azithromycin	0.06	>32	0.008–>32	60.0	1.2	38.8
Ceftaroline	0.015	0.12	≤0.008–>1	99.0		
Ceftriaxone	0.06	2	≤0.015–>2	76.6	11.2	12.2[b]
				87.8	10.2	2.0[c]
Clindamycin	≤0.25	>2	≤0.25–>2	71.1	0.3	28.6
Erythromycin	0.06	>32	≤0.015–>32	58.9	0.3	40.8
Levofloxacin	1	1	0.25–>4	98.1	0.3	1.6
Moxifloxacin	0.12	0.25	≤0.03–4	98.8	0.6	0.6
Penicillin	0.03	4	0.008–>8	53.8	22.5	23.8[d]
				53.8		46.2[e]
				86.9	10.9	2.2[f]
Tetracycline	0.5	>8	≤0.25–>8	60.9	0.3	38.8
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12–>4	61.9	10.9	27.2
***Staphylococcus aureus* (*n*=546)**						
Lefamulin	0.06	0.06	≤0.008–16	NA	NA	NA
Azithromycin	0.5	>32	0.03–>32	69.2	1.3	29.5
Ceftaroline	0.25	1	≤0.06–>8	92.9	6.6	0.5
Clindamycin	≤0.25	>2	≤0.25–>2	85.7	0.0	14.3
Doxycycline	≤0.06	0.5	≤0.06–8	96.0	4.0	0.0
Erythromycin	0.25	>8	≤0.06–>8	69.0	4.0	26.9
Gentamicin	≤1	>8	≤1–>8	88.6	0.5	10.8
Levofloxacin	0.25	>4	0.06–>4	80.8	0.4	18.9
Linezolid	1	1	0.25–2	100.0		0.0
Moxifloxacin	≤0.06	2	≤0.06–>4	81.1	3.7	15.2
Oxacillin	0.5	>2	≤0.25–>2	72.9		27.1
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	97.4		2.6
Vancomycin	1	1	0.25–2	100.0	0.0	0.0
***MRSA* (*n*=148)**						
Lefamulin	0.06	0.12	0.015–0.25	NA	NA	NA
Azithromycin	>32	>32	0.25–>32	35.8	0.7	63.5
Ceftaroline	1	2	0.25–>8	73.6	24.3	2.0
Clindamycin	≤0.25	>2	≤0.25–>2	51.4	0.0	48.6
Doxycycline	≤0.06	8	≤0.06–8	87.2	12.8	0.0
Erythromycin	>8	>8	≤0.06–>8	35.8	2.7	61.5
Gentamicin	≤1	>8	≤1–>8	64.2	0.7	35.1
Levofloxacin	>4	>4	0.12–>4	36.5	1.4	62.2
Linezolid	1	1	0.25–2	100.0		0.0
Moxifloxacin	2	>4	≤0.06–>4	37.8	10.8	51.4
Oxacillin	>2	>2	>2–>2	0.0		100.0
Trimethoprim-sulfamethoxazole	≤0.5	2	≤0.5–>4	90.5		9.5
Vancomycin	1	1	0.25–2	100.0	0.0	0.0

APAC=Asia-Pacific; CABP=community-acquired bacterial pneumonia; CLSI=Clinical and Laboratory Standards Institute; I=intermediate; LA=Latin America; 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)

H. influenzae

- Lefamulin demonstrated activity against *H. influenzae* in APAC and LA ($MIC_{50/90}$ of 0.5/1 µg/mL; **Table 2**) with 98.1% of all strains and 96.6% of β-lactamase positive strains inhibited at MIC ≤2 µg/mL
- *H. influenzae* isolates were susceptible (>80%) to most comparators, but resistance rates of 35.6% and 38.5% were reported for ampicillin and trimethoprim-sulfamethoxazole, respectively **(Table 2)**

M. catarrhalis

- 100% of *M. catarrhalis* isolates from APAC and LA were inhibited at lefamulin concentrations ≤0.12 µg/mL ($MIC_{50/90}$ of 0.06/0.12 µg/mL; **Table 2**)
- *M. catarrhalis* isolates were susceptible (>90%) to all comparators **(Table 2)**
- Nearly all *M. catarrhalis* isolates (98.0%) tested positive for β-lactamase

Table 2. Activity of Lefamulin and Comparators Against Gram-Negative Pathogens Commonly Causing CABP (APAC and LA Combined)

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Haemophilus influenzae* (*n*=104)**						
Lefamulin	0.5	1	0.06–8	NA	NA	NA
Amoxicillin-clavulanic acid	1	4	0.25–>8	93.3		6.7
Ampicillin	1	>8	0.12–>8	60.6	3.8	35.6
Azithromycin	0.5	2	0.12–>32	94.2		
Cefepime	0.12	0.25	0.03–>2	98.1		
Ceftriaxone	0.008	0.03	0.002–0.5	100.0		
Ciprofloxacin	0.015	0.015	0.008–>1	98.1		
Clarithromycin	8	16	1–>16	84.6	9.6	5.8
Moxifloxacin	0.03	0.03	0.008–>1	99.0		
Tetracycline	0.5	1	0.25–>8	97.1	0.0	2.9
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06–>4	60.6	1.0	38.5
***Moraxella catarrhalis* (*n*=49)**						
Lefamulin	0.06	0.12	0.015–0.12	NA	NA	NA
Amoxicillin-clavulanic acid	0.12	0.25	≤0.06–0.25	100.0		0.0
Azithromycin	0.015	0.03	0.008–0.06	100.0		
Ceftriaxone	0.25	1	0.008–1	100.0		
Clarithromycin	≤0.12	0.25	≤0.12–0.25	100.0		
Erythromycin	0.12	0.25	≤0.015–0.5	100.0		
Moxifloxacin	0.06	0.06	0.03–0.06			
Tetracycline	0.25	0.5	0.12–0.5	100.0	0.0	0.0
Trimethoprim-sulfamethoxazole	0.25	0.5	≤0.06–2	91.8	8.2	0.0

APAC=Asia-Pacific; CABP=community-acquired bacterial pneumonia; CLSI=Clinical and Laboratory Standards Institute; I=intermediate; LA=Latin America; 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

- Lefamulin demonstrated potent *in vitro* activity against pathogens that commonly cause CABP and that were collected in APAC and LA in 2016, including *S. pneumoniae, S. aureus* (including MRSA), *H. influenzae,* and *M. catarrhalis*
- Lefamulin's activity was unaffected by resistance to other antibiotic classes, including macrolides, lincosamides, β-lactams, fluoroquinolones, and tetracyclines
- Lefamulin may be an effective treatment option for CABP and warrants further development in the treatment of 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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