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In Vitro Activity of Lefamulin Against Bacterial Pathogens Collected From Patients With Community- or Hospital-Acquired Respiratory Tract Infections: 2016 SENTRY Data From Europe

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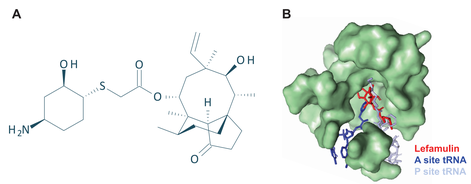
INTRODUCTION & PURPOSE

- Pneumonia poses a public health burden and is associated with significant morbidity and mortality, particularly in the very young and the elderly[1-3]
- Although the causes of pneumonia vary by geographic region and patient population, the most commonly isolated bacterial pathogen from community-acquired bacterial pneumonia (CABP) is *Streptococcus pneumoniae*. Other common pathogens include *Haemophilus influenzae*, *Moraxella catarrhalis*, *Staphylococcus aureus*, and the atypical respiratory pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*[4-7]
- Despite available antibiotics to treat bacterial pneumonia, new therapies are needed because antibiotic resistance rates are rising, some pathogens are naturally refractory to certain therapies, and traditionally used antibiotics have undesirable risks and side effects[8-10]
- Lefamulin is a novel semisynthetic pleuromutilin antibiotic that inhibits protein synthesis by binding to the 50S ribosomal subunit at the A- and P- sites in the peptidyl transferase center[11] **(Figure)**

Figure. (A) Structure of lefamulin and (B) lefamulin in the PTC



PTC=peptidyl transferase center

- A recent phase 3 trial for the treatment of CABP showed that lefamulin (150 mg intravenously [IV] every 12 hours [q12h] or 600 mg orally [PO] q12h for 7 days) was noninferior to moxifloxacin ± linezolid (400 mg IV q24h or 400 mg PO q24h for 7 days; if methicillin-resistant *S. aureus* was suspected, linezolid was added to moxifloxacin at 600 mg q12h IV or PO)
- Lefamulin has demonstrated activity against a variety of pathogens, including those commonly associated with CABP, and its activity is not influenced by resistance to other antimicrobial classes[7,12,13]
- The objective of this analysis was to evaluate the *in vitro* activities of lefamulin and comparators against a collection of bacterial respiratory pathogens from Europe in 2016

METHODS

- 1183 isolates were collected from patients with community-acquired respiratory infections (83.9%) and hospitalized patients with pneumonia (16.1%) in Europe (18 countries, 35 sites) as part of the SENTRY Antimicrobial Surveillance Program
- Lefamulin and comparators were tested by Clinical and Laboratory Standards Institute broth microdilution methods, and susceptibility was determined using the 2017 European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2017) breakpoints

RESULTS

- Lefamulin was the most active compound against *S. pneumoniae* (minimum concentrations at which 50% [MIC_{50}] and 90% [MIC_{90}] of the isolates were inhibited 0.06 and 0.12 mg/L, respectively; range, ≤0.008–1 mg/L) **(Table 1)**
  - *S. pneumoniae* isolates were largely susceptible to levofloxacin (98.2%) and ceftriaxone (88.1%). Resistance rates were higher for penicillin (28.6%), macrolides (22.2%), and tetracycline (19.9%), and resistance rates were even higher among penicillin-resistant *S. pneumoniae* (59.1% resistance to macrolides, 47.5% resistance to tetracyclines) **(Table 1)**
  - Lefamulin had potent *in vitro* activity against penicillin-nonsusceptible (penNS, *n*=221) and erythromycin-resistant (eryR, *n*=171) *S. pneumoniae* ($MIC_{50/90}$ for both, 0.06/0.12; range for both, ≤0.008–1 mg/L) **(Table 2)**
- Lefamulin also showed potent *in vitro* activity against *S. aureus* ($MIC_{50/90}$ of 0.06/0.12), *H. influenzae* ($MIC_{50/90}$ of 0.5/1; range, 0.015–4 mg/L), and *M. catarrhalis* ($MIC_{50/90}$ of 0.06/0.12; range, ≤0.008–0.12 mg/L) **(Table 3)**
  - 20.4% (44/216) of *H. influenzae* isolates were β-lactamase positive and were inhibited by lefamulin ($MIC_{50/90}$ of 0.5/1; range, 0.25–1 mg/L)
  - 96.5% (82/85) of *M. catarrhalis* isolates were β-lactamase positive and were inhibited by lefamulin ($MIC_{50/90}$ of 0.6/0.12; range, 0.015–0.12 mg/L)
- Lefamulin displayed potent antibacterial activity against this collection of respiratory pathogens (99.2% of isolates were inhibited at concentrations ≤1 mg/L) **(Tables 1, 2,** and **3)**

Table 1. Activity of Lefamulin and Comparators Against *S. pneumoniae*

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***S. pneumoniae* (*n*=772)**						
Lefamulin	**0.06**	**0.12**	**≤0.008–1**			
Amoxicillin-clavulanic acid	≤0.03	2	≤0.03–>4	–	–	–
Azithromycin	0.06	>32	0.004–>32	77.6	0.1	22.3
Ceftaroline	≤0.008	0.12	≤0.008–1	99.5	–	0.5
Ceftriaxone	0.03	1	≤0.015–>2	88.1	10.9	1
Clindamycin	≤0.25	>2	≤0.25–>2	85.1	–	14.9
Erythromycin	0.03	>32	≤0.015–>32	77.7	0.1	22.2
Levofloxacin	1	2	0.25–>4	98.2	–	1.8
Linezolid	1	2	0.25–2	100	0	0
Meropenem	0.015	0.5	≤0.008–>1	86.4 100	13.1 –	0.5[†] 0[‡]
Moxifloxacin	0.12	0.25	≤0.03–>4	98.6	–	1.4
Penicillin	0.015	2	≤0.004–>8	71.4 71.4	– 23.6	28.6[†] 5.1[‡]
Tetracycline	≤0.25	>8	≤0.25–>8	79.8	0.3	19.9
Tigecycline	0.03	0.06	0.015–0.25	–	–	–
Trimethoprim-sulfamethoxazole	0.25	4	≤0.12–>4	78.6	4.5	16.8
Vancomycin	0.25	0.5	≤0.06–0.5	100	–	0

EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MIC_{50}=minimum concentrations at which 50% of the isolates were inhibited; MIC_{90}=minimum concentrations at which 90% of the isolates were inhibited; S, susceptible.
*2017 EUCAST criteria.
[†]Using meningitis breakpoints.
[‡]Using nonmeningitis breakpoints.

RESULTS (continued)

Table 2. Activity of Lefamulin and Comparators Against Drug-Resistant *S. pneumoniae*

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
penNS *S. pneumoniae* (*n*=221)						
Lefamulin	**0.06**	**0.12**	**≤0.008–1**			
Amoxicillin-clavulanic acid	1	>4	≤0.03–>4	–	–	–
Azithromycin	8	>32	0.008–>32	40.5	0.5	59.1
Ceftaroline	0.06	0.12	≤0.008–1	98.2	–	1.8
Ceftriaxone	0.5	2	≤0.015–>2	58.4	38	3.6
Clindamycin	≤0.25	>2	≤0.25–>2	61.1	–	38.9
Erythromycin	8	>32	≤0.015–>32	41.2	0	58.8
Levofloxacin	1	1	0.25–>4	98.6	–	1.4
Linezolid	1	2	0.25–2	100	0	0
Meropenem	0.25	1	≤0.008–>1	52.5 100	45.7 –	1.8[†] 0[‡]
Moxifloxacin	0.12	0.25	≤0.03–>4	99.1	–	0.9
Penicillin	1	4	0.12–>8	0 0	– 82.4	100[†] 17.6[‡]
Tetracycline	0.5	>8	≤0.25–>8	52.5	0	47.5
Tigecycline	0.03	0.06	0.015–0.25	–	–	–
Trimethoprim-sulfamethoxazole	1	>4	≤0.12–>4	50.7	7.7	41.6
Vancomycin	0.25	0.5	0.12–0.5	100	–	0
eryR *S. pneumoniae* (*n*=171)						
Lefamulin	**0.06**	**0.12**	**≤0.008–1**			
Amoxicillin-clavulanic acid	0.5	>4	≤0.03–>4	–	–	–
Azithromycin	>32	>32	0.06–>32	1.2	0	98.8
Ceftaroline	0.06	0.25	≤0.008–1	97.7	–	2.3
Ceftriaxone	0.5	2	≤0.015–>2	59.6	35.7	4.7
Clindamycin	>2	>2	≤0.25–>2	32.7	–	67.3
Erythromycin	>32	>32	1–>32	0	0	100
Levofloxacin	1	2	0.25–>4	98.8	–	1.2
Linezolid	1	2	0.25–2	100	0	0
Meropenem	0.25	1	≤0.008–>1	57.3 100	40.9 –	1.8[†] 0[‡]
Moxifloxacin	0.12	0.25	≤0.03–>4	98.8	–	1.2
Penicillin	0.5	4	0.008–>8	24.0 24.0	– 59.6	76.0[†] 16.4[‡]
Tetracycline	>8	>8	≤0.25–>8	24.6	0	75.4
Tigecycline	0.03	0.06	0.015–0.25	–	–	–
Trimethoprim-sulfamethoxazole	1	>4	≤0.12–>4	57.3	5.8	36.8
Vancomycin	0.25	0.5	0.12–0.5	100	–	0

eryR=erythromycin-resistant (EUCAST 2017) *S. pneumoniae*; EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MIC_{50}=minimum concentrations at which 50% of the isolates were inhibited; MIC_{90}=minimum concentrations at which 90% of the isolates were inhibited; penNS=penicillin-nonsusceptible (EUCAST 2017, nonmeningitis) *S. pneumoniae*; S, susceptible.
*2017 EUCAST criteria.
[†]Using meningitis breakpoints.
[‡]Using nonmeningitis breakpoints.

RESULTS (continued)

Table 3. Activity of Lefamulin and Comparators for Pathogens Commonly Causing CABP

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***H. influenzae* (*n*=216)**						
Lefamulin	**0.5**	**1**	**0.015–4**			
Amoxicillin-clavulanic acid	0.5	2	0.12–4	96.3	–	3.7
Ampicillin	0.5	>8	0.12–>8	68.5	–	31.5[†]
Azithromycin	0.5	1	0.12–>32	0.9	98.1	0.9
Ceftriaxone	0.004	0.015	≤0.001–0.06	100	–	0
Moxifloxacin	0.03	0.03	0.008–>1	99.5	–	0.5
Tetracycline	0.5	1	0.25–>8	98.6	0.5	0.9
Tigecycline	0.12	0.25	0.06–1	–	–	–
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06–>4	64.8	0.9	34.3
***S. aureus* (*n*=110)**						
Lefamulin	**0.06**	**0.12**	**0.03–>16**			
Azithromycin	0.5	>32	0.06–>32	70	0.9	29.1
Ceftaroline	0.25	1	≤0.06–2	98.2	1.8	0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	93.6	0	6.4
Doxycycline	≤0.06	0.25	≤0.06–>8	96.4	1.8	1.8
Erythromycin	0.25	>8	≤0.06–>8	70	0.9	29.1
Linezolid	1	1	0.25–2	100	–	0
Moxifloxacin	≤0.06	4	≤0.06–>4	72.7	–	27.3
Oxacillin	0.5	>2	≤0.25–>2	69.1	–	30.9
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–1	100	0	0
Vancomycin	0.5	1	0.25–1	100	–	0
***M. catarrhalis* (*n*=85)**						
Lefamulin	**0.06**	**0.12**	**≤0.008–0.12**			
Amoxicillin-clavulanic acid	0.12	0.25	≤0.06–0.25	100	–	0
Azithromycin	0.015	0.03	0.008–0.03	100	0	0
Ceftriaxone	0.25	0.5	0.002–2	98.8	1.2	0
Erythromycin	0.12	0.25	0.03–0.25	100	0	0
Moxifloxacin	0.06	0.06	0.03–0.5	100	–	0
Trimethoprim-sulfamethoxazole	0.25	0.25	≤0.06–1	97.6	2.4	0

CABP=community-acquired bacterial pneumonia; EUCAST=European Committee on Antimicrobial Susceptibility Testing; MIC_{50}=minimum concentrations at which 50% of the isolates were inhibited; MIC_{90}=minimum concentrations at which 90% of the isolates were inhibited.
*2017 EUCAST criteria.
[†]β-lactamase test positive reported as resistant for penicillins without inhibitors.

CONCLUSIONS

- Lefamulin demonstrated potent *in vitro* activity against this contemporary collection of respiratory pathogens from Europe
- Lefamulin was active regardless of resistance phenotype to other antibiotic classes, including macrolides, β-lactams, tetracyclines, and fluoroquinolones
- These data support the continued clinical development of lefamulin for the treatment of CABP or other respiratory tract infections

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