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In Vitro Activity of Lefamulin against a Global Collection of Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CABP) - SENTRY 2015

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ABSTRACT

Background: CABP is the number one reason for death by infectious diseases worldwide and emerging resistance complicates its treatment. Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans. It is currently in Phase 3 trials for the treatment of CABP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) via four H-bonds and other interactions at the A- and P-site resulting in an "induced fit." This study investigated the activity of lefamulin and comparators against a contemporary set of bacterial pathogens associated with community-acquired respiratory infections collected worldwide.

Methods: Unique patients' isolates (n=2,817) were collected globally in the US (19.7%), Europe (36.9%), Latin America (5.7%) and Asia-Pacific region (37.6%) (30 countries, 116 sites) from adult and pediatric patients with respiratory tract infections (88.0%), bloodstream infections (5.5%) and other infections (2.4%). Lefamulin and comparators were tested by CLSI broth microdilution, and susceptibility was determined using the CLSI (2017) breakpoints.

Results: Lefamulin was the most potent compound tested with 99.7% of all *S. pneumoniae* isolates being inhibited at a concentration of ≤0.25 mg/L ($MIC_{50/90}$ values of 0.06/0.12 mg/L) and its activity was not affected by resistance to other antibiotic classes. *S. pneumoniae* isolates were largely susceptible to levofloxacin (99.1%) and ceftriaxone (96.5%), while 34.5%, 23.3% and 16.8% of isolates were resistant to macrolides, tetracycline and clindamycin, respectively. Lefamulin also showed potent activity against *H. influenzae* ($MIC_{50/90}$ of 0.5/1 mg/L), including 22.0% of ß-lactamase-producing strains and *M. catarrhalis* (0.06/0.12 mg/L).

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

Table 1. *In vitro* activity of lefamulin and comparators

Organism	*n*	$MIC_{50/90}$ [mg/L] Lefamulin	Amoxicillin Clavulanic acid	Cef-triaxone	Azithro-mycin	Levo-floxacin	Tetra-cycline
S. pneumoniae	1835	0.06 / 0.12	≤0.03 / 2	0.03 / 1	0.06 / >4	1 / 1	0.25 / >4
Penicillin non-susceptible [a]	644	0.06 / 0.12	1 / >4	0.5 / 1	>4 / >4	1 / 1	>4 / >4
Penicillin resistant	195	0.06 / 0.12	4 / >4	1 / 2	>4 / >4	1 / 1	>4 / >4
Macrolide resistant	633	0.06 / 0.12	0.5 / 4	0.25 / 1	>4 / >4	1 / 1	>4 / >4
H. influenzae	536	0.5 / 1	0.5 / 2	≤0.015 / ≤0.015	1 / 1	≤0.015 / ≤0.015	0.5 / 0.5
ß-lactamase positive	118	0.5 / 1	1 / 2	≤0.015 / ≤0.015	0.5 / 1	≤0.015 / ≤0.015	0.5 / 0.5
M. catarrhalis	446	0.06 / 0.12	0.12 / 0.25	0.25 / 0.5	0.015 / 0.03	0.03 / 0.03	0.25 / 0.25

[a] Used oral penicillin breakpoints of ≥2 mg/L for resistant and 0.12-1 mg/L for intermediate according to CLSI (2017)

INTRODUCTION

Community-acquired bacterial pneumonia (CABP) is a major cause of adult and child mortality globally with 3.2 million deaths in 2015 and an estimate of 3.5 million in 2030.[1] The aetiology of CABP includes *Streptococcus pneumoniae, Mycoplasma pneumoniae, Chlamydophila pneumoniae,* and *Haemophilus influenzae* as significant aetiological agents.[1,2] Increasing resistance rates to commonly used antibiotics complicate treatment, increase the severity of disease and often prolong hospital stays.[1,2]

Lefamulin is the first representative of pleuromutilin class in clinical development for systemic administration in humans. Pleuromutilins inhibit bacterial protein synthesis of Gram-positive and Gram-negative organisms as well as atypical respiratory pathogens. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) via four H-bonds and other interactions at the A- and P-sites resulting in an "induced fit."[3,4] (Figure 1) Lefamulin's antibacterial profile includes activity against atypical respiratory pathogens (Table 2).[5,6] Phase 1 and 2 trials have demonstrated that IV and oral administration of lefamulin are well tolerated. Furthermore, lefamulin (100 mg or 150 mg IV q12 hours) showed similar efficacy to IV vancomycin in a clinical Phase 2 trial in patients with acute bacterial skin and skin structure infections.[7] Currently, lefamulin is in late-stage development for the treatment of CABP.

This study investigated the activity of lefamulin and comparators against a contemporary, global set of typical bacterial pathogens that commonly cause CABP.

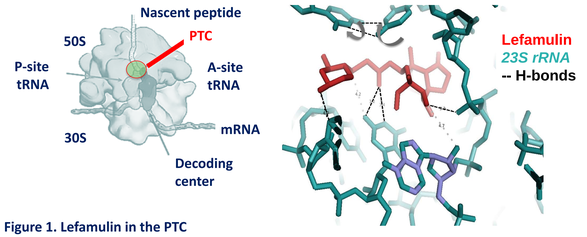

Figure 1. Lefamulin in the PTC
Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) via four H-bonds and other interactions at the A- and P-sites, resulting in an "induced fit." [3,4]

Table 2. *In vitro* activity of lefamulin against *Mycoplasma pneumoniae* [5]

M. pneumoniae	*n*	MIC_{50} [mg/L]	MIC_{90} [mg/L]	Range [mg/L]
Lefamulin	60	≤0.001	0.002	≤0.001 - 0.008
Azithromycin	60	16	>32	≤0.001 - >32
Moxifloxacin	50	0.125	0.25	0.063 - 0.25
Tetracycline	50	0.5	1	0.25 - 1

RESULTS

- Lefamulin displayed potent antibacterial activity against this global collection of contemporary pathogens collected from patients with predominantly respiratory tract infections (Table 3).

Table 3. Susceptibility of CABP pathogens to lefamulin and comparators [mg/L]

Organism (*n*)	MIC_{50}	MIC_{90}	MIC_{99}	Range [mg/L]	% S [a]	% I [a]	% R [a]
***S. pneumoniae* (*1,835*)**							
Lefamulin	**0.06**	**0.12**	**0.25**	**≤0.008 - 1**	-	-	-
Amoxicillin-clavulanic acid	≤0.03	2	>4	≤0.03 - >4	93.8	2.9	3.3
Azithromycin	0.06	>4	>4	≤0.03 - >4	65.4	0.4	34.2
Ceftaroline	≤0.008	0.12	>1	≤0.008 - >1	99.9	-	-
Ceftriaxone	0.03	1	>2	≤0.015 - >2	96.5	2.6	0.9 [b]
Clindamycin	≤0.12	>1	>1	≤0.12 - >1	82.4	0.8	16.8
Cotrimoxazole	≤0.5	>4	>4	≤0.5 - >4	70.8	11.3	17.9
Erythromycin	0.03	>2	>2	≤0.015 - >2	65.2	0.3	34.5
Levofloxacin	1	1	2	≤0.12 - >4	99.1	0.1	0.9
Penicillin	≤0.06	2	4	≤0.06 - 8	64.9	24.5	10.6 [b]
Tetracycline	0.25	>4	>4	≤0.12 - >4	76.1	0.6	23.3
***H. influenzae* (*536*)**							
Lefamulin	**0.5**	**1**	**2**	**≤0.12 - 4**	-	-	-
Amoxicillin-clavulanic acid	0.5	2	8	≤0.12 - 16	97.6	-	2.4
Ampicillin	0.5	>8	>8	0.12 - >8	74.6	1.5	23.9 [c]
Azithromycin	1	1	4	0.12 - >4	99.1	-	-
Ceftriaxone	≤0.015	≤0.015	0.25	≤0.015 - 0.25	100.0	-	-
Clarithromycin	8	8	>16	0.5 - >16	92.4	6.2	1.5
Cotrimoxazole	0.06	>4	>4	≤0.03 - >4	67.9	4.7	27.4
Levofloxacin	≤0.015	≤0.015	0.5	≤0.015 - >2	99.6	-	-
Tetracycline	0.5	0.5	16	≤0.12 - >16	97.8	0.2	2.1
***M. catarrhalis* (*446*)**							
Lefamulin	**0.06**	**0.12**	**0.12**	**≤0.008 - 0.25**	-	-	-
Amoxicillin-clavulanic acid	0.12	0.25	0.25	≤0.03 - 0.25	100.0	-	0.0
Azithromycin	0.015	0.03	0.06	0.002 - 0.06	100.0	-	-
Ceftriaxone	0.25	0.5	1	≤0.015 - 1	100.0	-	-
Erythromycin	0.12	0.12	0.5	≤0.015 - 1	100.0	-	-
Levofloxacin	0.03	0.03	0.06	≤0.015 - 1	100.0	-	-
Tetracycline	0.25	0.25	0.25	≤0.03 - 0.5	100.0	0.0	0.0

[a] Criteria as published by CLSI [2017][7]
[b] Non-meningitis breakpoints applied for penicillin
[c] ß-lactamase positive, reported as resistant for penicillins without inhibitors

RESULTS continued

- Lefamulin was one of the most active compounds against *S. pneumoniae* ($MIC_{50/90}$ of 0.06/0.12 mg/L) with 99.9% of isolates inhibited at a lefamulin concentration of 0.5 mg/L.
  - *S. pneumoniae* isolates were largely susceptible to ceftaroline (99.9%), ceftriaxone (96.5%) and levofloxacin (99.1%) , whereas 34.5% and 23.3% of isolates were resistant to macrolides and tetracycline, respectively.
- Lefamulin's activity was not affected by resistance to other antibiotic classes (Table 1)
  - 100% of *S. pneumoniae* resistant to penicillin (*n*=195, oral breakpoint ≥ 2 mg/L) were inhibited by lefamulin concentrations of ≤0.25 mg/L; ($MIC_{50/90}$ of 0.06/0.12 mg/L) whereas 86.7% and 73.3% were resistant to macrolides and tetracyclines, respectively.
  - 99.1% of macrolide-resistant *S. pneumoniae* (*n*=633) were inhibited by ≤0.25 mg/L of lefamulin ($MIC_{50/90}$ 0.06/0.12 mg/L, range 0.008-1 mg/L)
- Against *H. influenzae* and *M. catarrhalis*, lefamulin also displayed potent activity, including ß-lactamase-producing strains.
  - *H. influenzae*, $MIC_{50/90}$ of 1/2 mg/L (23.9% ß-lactamase producing)
  - *M. catarrhalis*, $MIC_{50/90}$ of 0.06/0.12 mg/L

CONCLUSIONS

- **Lefamulin demonstrated potent *in vitro* activity against this contemporary global collection of respiratory pathogens regardless of resistance phenotype to the other antibiotic classes including macrolides, ß-lactams, tetracyclines or fluoroquinolones.**
- **Results are consistent with those obtained from previous studies, including a variety of *S. pneumoniae* serotypes.[9]**
- **These data support the continued clinical development of lefamulin for the treatment of respiratory tract infections, including CABP.**

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