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In Vitro Activity of Lefamulin against Bacterial Pathogens Commonly Causing Community-Acquired Bacterial Pneumonia (CAP): 2015 SENTRY Data from Europe

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INTRODUCTION & PURPOSE

Background: 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 CAP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the peptidyl transferase center (PTC) at two sites. It interacts via four H-bonds and other interactions resulting in an "induced fit" whereby nucleotides in the PTC shift and further tighten the binding pocket around lefamulin (Figure 1).[1,2]

Lefamulin has demonstrated potent *in vitro* activity against a variety of pathogens that cause skin and soft tissue infections and respiratory tract infections caused by Gram positive, fastidious Gram-negative, and atypical bacteria including *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila*.[3,4] Lefamulin showed similar efficacy to IV vancomycin in a clinical Phase 2 trial in patients with acute bacterial skin and skin structure infections.[5] Furthermore, lefamulin has been well tolerated in phase 1 and phase 2 trials.

CAP is the number one infectious diseases cause of death worldwide and emerging resistance complicates its treatment.[6] This study investigated the activity of lefamulin and comparators against a contemporary set of bacterial respiratory pathogens collected in Europe.

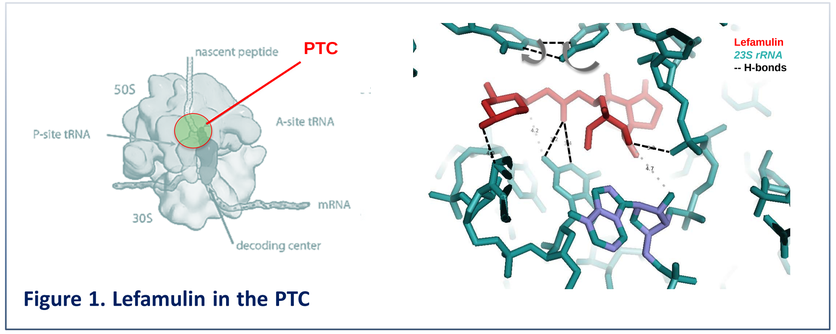

Figure 1. Lefamulin in the PTC

METHODS

Unique patients' isolates (*n*=1040) were collected in Europe (19 countries, 36 sites) from patients with respiratory tract infections (87.5%), blood stream infections (8.4%) and other infections (4.1%). Only one isolate per patient infection episode was included in surveillance.

Lefamulin and comparators were tested by CLSI broth microdilution methods and susceptibility was determined using the EUCAST (2017) breakpoints.[7,8] QC reference organisms were tested concurrently for lefamulin and comparator agents.

RESULTS

- Lefamulin displayed potent antibacterial activity against this collection of respiratory pathogens with all 1040 isolates inhibited at concentrations of ≤2 mg/L (Table 1).
- Lefamulin was the most active compound against *S. pneumoniae* ($MIC_{50/90}$ of 0.06/0.12 mg/L) with only 3 isolates inhibited by a lefamulin concentration of ≥ 0.5 µg/mL
  - *S. pneumoniae* isolates were susceptible to levofloxacin (98.6%), whereas 27.6%, 24.6% and 13.2% of isolates were resistant to macrolides, tetracycline, and ceftriaxone, respectively.

Table 1. Susceptibility of CABP pathogens against lefamulin and comparators

Organism (*N*)	MIC_{50}	MIC_{90}	MIC_{99}	Range	% Susceptible[a]	% Intermediate[a]	% Resistant[a]
***S. pneumoniae* (710)**							
Lefamulin	**0.06**	**0.12**	**0.25**	**≤0.008 to 1**			
Amoxicillin-clavulanic acid	≤0.03	2	>4	≤0.03 to >4			
Azithromycin	0.06	>4	>4	≤0.03 to >4	72.1	0.3	**27.6**
Ceftaroline	≤0.008	0.12	0.25	≤0.008 to 0.25	100.0		0.0
Ceftriaxone	0.03	1	2	≤0.015 to >2	86.8	12.5	0.7
Clindamycin	≤0.12	>1	>1	≤0.12 to >1	81.0		**19.0**
Erythromycin	0.03	>2	>2	≤0.015 to >2	72.3	0.1	**27.6**
Imipenem	≤0.015	0.25	0.5	≤0.015 to 0.5	100.0		0.0
Levofloxacin	1	1	>4	≤0.12 to >4	98.6		1.4
Penicillin	≤0.06	2	4	≤0.06 to 8	68.6	27.3	4.1 [b]
Tetracycline	0.25	>4	>4	≤0.12 to >4	74.8	0.6	**24.6**
***H. influenzae* (170)**							
Lefamulin	**0.5**	**1**	**2**	**≤0.12 to 2**			
Amoxicillin-clavulanic acid	0.5	2	4	≤0.12 to 8	97.6		2.4
Ampicillin	0.25	8	>8	0.12 to >8	84.7		**15.3** [c]
Azithromycin	0.5	1	2	0.12 to 2	1.2	98.8	0.0
Ceftriaxone	≤0.015	≤0.015	0.06	≤0.015 to 0.06	100.0		0.0
Clarithromycin	4	8	16	1 to 16	2.4	97.6	0.0
Levofloxacin	≤0.015	≤0.015	0.5	≤0.015 to 0.5	98.2		1.8
Tetracycline	0.5	0.5	0.5	≤0.12 to >16	99.4	0.0	0.6
Trimethoprim-sulfamethoxazole	0.06	>4	>4	≤0.03 to >4	74.7	2.9	**22.4**
***M. catarrhalis* (160)**							
Lefamulin	**0.06**	**0.12**	**0.12**	**≤0.008 to 0.12**			
Amoxicillin-clavulanic acid	0.12	0.25	0.25	≤0.03 to 0.25	100.0		0.0
Azithromycin	0.015	0.03	0.06	0.002 to 0.06	100.0	0.0	0.0
Ceftriaxone	0.25	0.5	0.5	≤0.015 to 1	100.0	0.0	0.0
Erythromycin	0.12	0.12	0.5	≤0.015 to 1	98.8	0.6	0.6
Levofloxacin	0.03	0.06	0.06	≤0.015 to 0.5	100.0		0.0
Tetracycline	0.12	0.25	0.5	≤0.03 to 0.5	100.0	0.0	0.0

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

RESULTS (con't)

- Lefamulin's activity was not affected by resistance to other antibiotic classes.
  - $MIC_{50/90}$ of lefamulin against penicillin non-susceptible *S. pneumoniae* (*n*=223, non-meningitis breakpoint of >0.06 µg/mL) were 0.06/0.12 µg/mL
  - 100% of *S. pneumoniae* resistant to penicillin (*n*=29, breakpoint >2 µg/mL) were inhibited by lefamulin concentrations of ≤0.12 µg/mL;
    - PRSP showed high resistance rates to macrolides (93.1%), tetracycline (89.7%), amoxicillin-clavulanic acid (62.1%) and trimethoprim-sulfamethoxazole (96.6%) whereas PRSP were largely susceptible to levofloxacin (82.8%), tigecycline (100%) and vancomycin (100%).
  - 98.5% of macrolide-resistant *S. pneumoniae* (*n*=196) were inhibited by ≤0.25 µg/mL lefamulin ($MIC_{50/90}$ 0.06/0.12 µg/mL, range 0.008-1 µg/mL)
- Against the fastidious respiratory pathogens, lefamulin showed potent activity and was not affected by ß-lactamase production.
  - *H. influenzae*, $MIC_{50/90}$ of 0.5/1 mg/L, including 12.9% of ß-lactamase producing strains
  - *M. catarrhalis,* $MIC_{50/90}$ of 0.06/0.12 mg/L

CONCLUSIONS

- **Lefamulin demonstrated potent *in vitro* activity against a contemporary collection of respiratory pathogens from Europe.**
- **Lefamulin was active regardless of resistance phenotype to the other antibiotic classes including macrolides, ß-lactams, tetracyclines or fluoroquinolones.**
- **The lefamulin activity against this contemporary collection is consistent with results 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 CAP.**

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