Saturday – 644

In Vitro Activity of Lefamulin Against Bacterial Pathogens Commonly Causing Community-Acquired Respiratory Tract Infections (CARTI) – Global SENTRY Surveillance 2016

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ABSTRACT*

Background: Lefamulin (LEF) is the first semisynthetic pleuromutilin antibiotic for IV and oral use in humans and has recently completed a phase 3 clinical trial for the treatment of CABP in adults where it demonstrated noninferiority to moxifloxacin ± linezolid. LEF effectively and selectively inhibits bacterial translation. This study investigated the activity of LEF and comparators against a contemporary set of bacterial respiratory pathogens collected worldwide.

Methods: Unique isolates (*n*=2684) were collected globally (30 countries, 88 sites) from patients with CARTI. LEF and comparators were tested by CLSI broth microdilution methods, and susceptibility was determined using CLSI (2018) breakpoints.

Results: LEF showed potent *in vitro* activity against this collection of respiratory pathogens, with 99.9% of *Streptococcus pneumoniae* inhibited at ≤0.5 µg/mL. Isolates were highly susceptible to moxifloxacin (98.8%), ceftriaxone (95.4%), and amoxicillin-clavulanic acid (93.3%), whereas only 64.9% and 65.1% were susceptible to azithromycin and penicillin (MIC ≥2 µg/mL), respectively. LEF was also active against *Staphylococcus aureus* with 99.2% of all isolates being inhibited at 0.25 µg/mL LEF. The 27.4% of *S. aureus* that were oxacillin-resistant (methicillin-resistant [MRSA]) showed particularly high resistance rates to erythromycin (52.9%), moxifloxacin (52.9%), and clindamycin (26.5%). *Haemophilus influenzae* (99.1% inhibited at LEF ≤2 µg/mL) and *Moraxella catarrhalis* (100.0% inhibited at LEF ≤0.12 µg/mL) were largely susceptible to the comparators, except for ampicillin (64.1% susceptible among *H. influenzae*) and trimethoprim-sulfamethoxazole (63.3% susceptible among *H. influenzae*).

Conclusion: LEF was highly active against pathogens collected globally from CABP patients in 2016, and its activity was not affected by resistance to other antibiotic classes. These data support the ongoing development of LEF for the treatment of CABP.

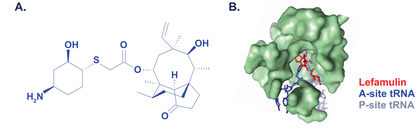
*Amended

INTRODUCTION

- Pneumonia is a major cause of morbidity and mortality in adults and children[1]
- The most commonly isolated bacterial pathogen from community-acquired bacterial pneumonia (CABP) is *Streptococcus pneumoniae*, followed by other pathogens, including *Staphylococcus aureus*, *Haemophilus influenzae*, and *Moraxella catarrhalis*, and the atypical pathogens *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae*, and *Legionella pneumophila*[2-5]
- Given the rising rates of antibiotic resistance among organisms causing CABP,[6] there is a need for new antimicrobial therapies
- Lefamulin is a semisynthetic pleuromutilin antibiotic in clinical development. Lefamulin inhibits bacterial protein synthesis in Gram-positive and Gram-negative organisms and atypical pathogens by binding to the peptidyl transferase center of the 50S ribosomal subunit[7,8] **(Figure 1)**
- Lefamulin was evaluated in two Lefamulin Evaluation Against Pneumonia (LEAP 1 and LEAP 2) phase 3 trials in adults with CABP. In both trials intravenous and oral lefamulin demonstrated noninferiority to moxifloxacin ± linezolid
- The objective of this analysis was to investigate the activity of lefamulin and comparators against a contemporary set of pathogens collected worldwide that commonly cause CABP. This poster provides an update on the analysis presented in the abstract

INTRODUCTION (continued)

Figure 1. Structure of Lefamulin (A) in the Peptidyl Transferase Center (B)



METHODS

- 4505 unique pathogens commonly causing CABP were isolated globally in 2016 as a part of the SENTRY Antimicrobial Surveillance Program
  - Of those, 2838 isolates were collected from hospitalized patients with pneumonia or patients with a respiratory tract infection (30 countries, 88 sites): *S. aureus* (*n*=312), *S. pneumoniae* (*n*=1774), *H. influenzae* (*n*=532), and *M. catarrhalis* (*n*=220)
- Lefamulin and comparators were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution methods, and susceptibility was determined using CLSI (2018) breakpoints

RESULTS

- Lefamulin was among the most potent compounds against *S. pneumoniae* with a minimum inhibitory concentration required to inhibit 50% and 90% of isolates ($MIC_{50/90}$) of 0.06/0.12 µg/mL (range, ≤0.008–1 µg/mL; **Table 1**)
  - 99.9% of *S. pneumoniae* isolates were inhibited at ≤0.5 µg/mL
  - Lefamulin activity was not affected by resistance to other antibiotic classes **(Table 1)**; penicillin-intermediate (*n*=100) and -resistant (*n*=12) *S. pneumoniae* isolates maintained the same lefamulin $MIC_{50/90}$ values (0.06/0.12 µg/mL) as penicillin-susceptible isolates (*n*=1976)
  - *S. pneumoniae* isolates were largely susceptible to moxifloxacin (98.9%), ceftriaxone (95.6%), and amoxicillin/clavulanic acid (93.5%), whereas only 66.0% were susceptible to azithromycin
- Lefamulin was also active against *S. aureus* ($MIC_{50/90}$ of 0.6/0.12 µg/mL) with 99.6% of all isolates and 99.4% of methicillin-resistant *S. aureus* (MRSA; oxacillin-resistant) being inhibited at ≤0.25 µg/mL of lefamulin
  - The 32.6% of *S. aureus* identified as MRSA showed particularly high resistance rates to azithromycin (72.2%), erythromycin (68.7%), moxifloxacin (51.9%), and clindamycin (34.1%)
- Lefamulin demonstrated activity against *H. influenzae* ($MIC_{50/90}$ of 0.5/1 µg/mL; **Table 2**), and its activity was unaffected by β-lactamase production, with 99.1% of all isolates being inhibited at ≤2 µg/mL of lefamulin
  - *H. influenzae* isolates were largely susceptible to the comparators, except for ampicillin (26.5% resistant) and trimethoprim-sulfamethoxazole (34.4% resistant)
- 100% of *M. catarrhalis* isolates were inhibited at lefamulin concentrations of ≤0.12 µg/mL ($MIC_{50/90}$ of 0.6/0.12 µg/mL; **Table 2**)
  - *M. catarrhalis*, including β-lactamase positive isolates, were susceptible to comparator antibiotics

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
***S. pneumoniae* (*n*=2088)**						
Lefamulin	0.06	0.12	≤0.008–1	NA	NA	NA
Amoxicillin-clavulanic acid	≤0.03	2	≤0.03–>4	93.5	2.9	3.6
Azithromycin	0.06	>32	0.004–>32	66.0	1.0	33.0
Ceftaroline	≤0.008	0.12	≤0.008–1	99.8	–	–
Ceftriaxone	0.03	1	≤0.015–>2	85.6	10.0	4.4[b]
				95.6	3.4	1.0[c]
Clindamycin	≤0.25	>2	≤0.25–>2	83.0	0.3	16.7
Erythromycin	0.06	>32	≤0.015–>32	65.7	0.4	33.8
Levofloxacin	1	1	0.25–>4	98.6	0.2	1.2
Linezolid	1	2	0.25–2	100.0	0.0	0.0
Meropenem	0.015	0.5	≤0.008–>1	83.1	9.7	7.2
Moxifloxacin	0.12	0.25	≤0.03–>4	98.9	0.5	0.6
Penicillin	0.003	2	≤0.004–>8	66.3	20.5	13.2[d]
				66.3	0.0	33.7[e]
				94.6	4.8	0.6[f]
Tetracycline	≤0.25	>8	≤0.25–>8	77.2	0.4	22.4
Trimethoprim-sulfamethoxazole	0.25	>4	≤0.12–>4	71.4	10.3	18.3
Vancomycin	0.25	0.5	≤0.06–0.5	100.0	0.0	0.0
***S. aureus* (*n*=1646)**						
Lefamulin	0.06	0.12	≤0.008–>16	NA	NA	NA
Azithromycin	0.5	>32	0.03–>32	61.3	1.0	37.7
Ceftaroline	0.25	1	≤0.06–>8	96.4	3.5	0.2
Clindamycin	≤0.25	>2	≤0.25–>2	87.2	0.2	12.6
Doxycycline	≤0.06	0.25	≤0.06–>8	98.2	1.8	0.1
Erythromycin	0.25	>8	≤0.06–>8	60.9	5.5	33.6
Gentamicin	≤1	≤1	≤1–>8	93.4	0.5	6.1
Levofloxacin	0.25	>4	≤0.03–>4	73.0	1.0	26.0
Linezolid	1	1	≤0.12–2	100.0	0.0	0.0
Moxifloxacin	≤0.06	4	≤0.06–>4	73.4	7.5	19.1
Oxacillin	0.5	>2	≤0.25–>2	67.4	0.0	32.6
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	98.2	0.0	1.8
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0

I=intermediate; 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.

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
***H. influenzae* (*n*=550)**						
Lefamulin	0.5	1	0.015–8	NA	NA	NA
Amoxicillin-clavulanic acid	1	2	0.12–>8	98.4	0.0	1.6
Ampicillin	1	>8	0.12–>8	64.9	8.5	26.5
Azithromycin	0.5	1	0.12–>32	98.5	–	–
Cefepime	0.06	0.25	≤0.015–>2	99.6	–	–
Ceftriaxone	0.004	0.015	≤0.001–0.5	100.0	0.0	0.0
Ciprofloxacin	0.015	0.015	0.004–>1	99.3	–	–
Clarithromycin	8	8	0.25–>16	91.5	6.5	2.0
Levofloxacin	0.015	0.03	0.008–>2	99.6	–	–
Moxifloxacin	0.03	0.03	0.008–>1	99.6	–	–
Tetracycline	0.5	1	0.25–>8	98.9	0.0	1.1
Tigecycline	0.12	0.25	0.06–1	98.0	–	–
Trimethoprim-sulfamethoxazole	0.12	>4	≤0.06–>4	63.5	2.2	34.4
***M. catarrhalis* (*n*=221)**						
Lefamulin	0.06	0.12	≤0.008–0.12	NA	NA	NA
Amoxicillin-clavulanic acid	0.12	0.25	≤0.06–0.5	100.0	0.0	0.0
Azithromycin	0.015	0.03	0.008–0.06	100.0	0.0	0.0
Ceftriaxone	0.25	0.5	0.002–2	100.0	0.0	0.0
Clarithromycin	≤0.12	0.25	≤0.12–0.25	100.0	0.0	0.0
Erythromycin	0.12	0.25	≤0.015–0.5	100.0	0.0	0.0
Imipenem	≤0.03	0.06	≤0.03–0.12	–	–	–
Levofloxacin	0.06	0.06	0.015–1	100.0	0.0	0.0
Meropenem	≤0.008	≤0.008	≤0.008–0.015	–	–	–
Moxifloxacin	0.06	0.06	0.03–0.5	–	–	–
Tetracycline	0.25	0.5	0.12–0.5	100.0	0.0	0.0
Tigecycline	0.06	0.06	0.03–0.12	–	–	–
Trimethoprim-sulfamethoxazole	0.12	0.25	≤0.06–2	95.9	4.1	0.0

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

CONCLUSIONS

- Lefamulin was highly active against pathogens commonly causing CABP collected globally in 2016
- Lefamulin's activity was unaffected by resistance phenotypes to other antibiotic classes, including macrolides, β-lactams, fluoroquinolones, and lincosamides
- 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. Jennifer M. Streit, 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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