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In Vitro Activity of Lefamulin Against Bacterial Pathogens Commonly Causing Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Bloodstream Infections (BSI): 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 has further shown potent efficacy in a phase 2 clinical trial in ABSSSI being comparable to vancomycin. This study investigated the activity of LEF and comparators against a contemporary collection of bacteria commonly causing ABSSSI and BSI worldwide.

Methods: Unique isolates (*n*=2488) were collected globally (31 countries, 94 sites) from patients with ABSSSI (837), BSI (1130), pneumonia (346), and other infections. 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 *Staphylococcus aureus* with 99.1% inhibited at ≤0.12 µg/mL ($MIC_{50/90}$ of 0.06/0.12 µg/mL). 32.6% of the *S. aureus* isolates were oxacillin-resistant (MRSA), which showed particularly high resistance rates to macrolides (68.7%), levofloxacin (68.7%), and clindamycin (34.1%). LEF was similarly active against coagulase-negative staphylococci (of which 72.8% were oxacillin-resistant). 99.4% of all ß-hemolytic streptococci isolates were inhibited by 0.25 µg/mL of LEF. LEF also displayed activity against viridans group streptococci (VGS; LEF $MIC_{50/90}$ of 0.06/1 µg/mL). ß-hemolytic streptococci and VGS were largely susceptible to the tested comparators, except for erythromycin (70.8% S) and clindamycin (86.6% S).

Conclusions: LEF was highly active against this contemporary collection of pathogens commonly causing ABSSSI and BSI, and its activity was not affected by resistance to other antibiotic classes. These data support the continued development of LEF for the treatment of ABSSSI and further exploration of LEF activity in BSI.

*Amended

INTRODUCTION

- *Staphylococcus aureus* and *Streptococcus pyogenes* are the predominant causative pathogens for acute bacterial skin and skin structure infections (ABSSSI). *S. aureus* is additionally implicated in a wide spectrum of infections including bloodstream infections (BSI)[1-3]
- With increasing antibiotic resistance among pathogens, hospitalizations for ABSSSI and BSI continue to rise in the United States and contribute to substantial economic burden, creating an urgent need for novel antibiotics[1,2,4,5]
- Lefamulin is the first pleuromutilin antibiotic for intravenous and oral use in humans.[6] It inhibits bacterial protein synthesis by specific interaction with the A- and P-sites in the peptidyl transferase center of the 50S ribosomal subunit
- Lefamulin has recently demonstrated noninferiority to moxifloxacin ± linezolid in two phase 3 clinical trials for the treatment of community-acquired bacterial pneumonia
- Lefamulin has further shown efficacy comparable to vancomycin in a phase 2 clinical trial in patients with ABSSSI caused by Gram-positive pathogens, including methicillin-resistant *S. aureus* (MRSA)[7]
- The objective of this study was to investigate the *in vitro* activity of lefamulin and comparators against a contemporary collection of bacteria commonly causing ABSSSI and BSI worldwide

METHODS

- A total of 2488 isolates of *S. aureus* (*n*=1646), coagulase-negative staphylococci (CoNS; *n*=276), ß-hemolytic streptococci (*n*=389), and viridans group streptococci (*n*=177) were collected from medical centers worldwide in 2016 as part of the SENTRY Antimicrobial Surveillance Program
  - Isolates were collected from patients with BSI (*n*=1130, 45.4%), ABSSSI (*n*=837, 33.6%), pneumonia (*n*=346, 13.9%), urinary tract infections (*n*=25, 1%), intra-abdominal infections (*n*=20, 0.8%), and other infections (*n*=130, 5.2%)
- Antibacterial activity was assessed using Clinical and Laboratory Standards Institute (CLSI) broth microdilution methodology using cation-adjusted Mueller-Hinton broth (CA-MHB)
- Minimum inhibitory concentration (MIC) values for lefamulin and comparator antibacterial agents were determined using CLSI guidelines (www.clsi.org); susceptibility was interpreted per CLSI (2018) breakpoints
- Quality control organisms were tested as controls per CLSI recommendation

RESULTS

- Lefamulin demonstrated potent antibacterial activity against *S. aureus* with 99.1% of isolates inhibited at ≤0.12 µg/mL (minimum inhibitory concentration required to inhibit 50% [MIC_{50}] and 90% [MIC_{90}] of isolates; $MIC_{50/90}$ of 0.06/0.12 µg/mL; **Table 1**)
  - Susceptibility rates were 100% for daptomycin ($MIC_{50/90}$ of 0.5/0.5 µg/mL), linezolid (1/1), teicoplanin (≤0.5/≤0.5), tigecycline (0.06/0.12), and vancomycin (0.5/1)
  - 32.6% and 33.6% of *S. aureus* isolates were resistant to oxacillin (MRSA) and erythromycin
- Among MRSA isolates, higher rates of resistance were seen for macrolides and fluoroquinolones **(Table 1)**
  - 68.7%, 72.2%, and 51.9% of MRSA were resistant to erythromycin, azithromycin, and moxifloxacin, respectively
- The activity of lefamulin against *S. aureus* was not affected by resistance to methicillin ($MIC_{50/90}$ of 0.06/0.12; **Table 1** and **Figure 1**)
- Lefamulin was one of the most active compounds against CoNS isolates ($MIC_{50/90}$ of 0.03/0.06 µg/mL; 97.8% inhibited at ≤2 µg/mL; **Table 2**)
- The majority of CoNS isolates were susceptible to daptomycin, doxycycline, linezolid, and vancomycin; however, moderate to high resistance rates were seen for clindamycin (29.0%), erythromycin (60.9%), levofloxacin (48.6%), moxifloxacin (36.6%), and oxacillin (72.8%; **Table 2**)
- Lefamulin was active against ß-hemolytic streptococci; 99.2% of the isolates were inhibited at ≤0.12 µg/mL ($MIC_{50/90}$ of 0.03/0.03 µg/mL)
  - Lefamulin was highly active against *S. pyogenes* and *Streptococcus agalactiae* ($MIC_{50/90}$ of 0.015/0.03 and 0.03/0.03 µg/mL, respectively; **Table 2**)
- All ß-hemolytic streptococci isolates were susceptible to ceftriaxone, linezolid, penicillin, and vancomycin, while moderate resistance rates were seen for clindamycin (13.6%) and erythromycin (25.0%; **Table 2**)

Figure 1. MIC Distributions of Lefamulin for *Staphylococcus aureus* Isolates Collected From Medical Centers Worldwide in 2016

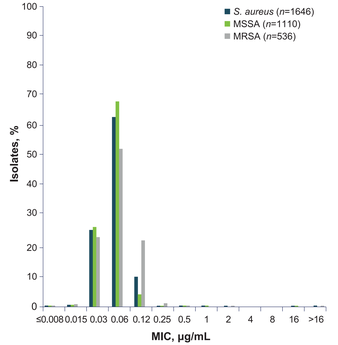

Table 1. Activity of Lefamulin and Comparator Agents Against *Staphylococcus aureus*

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***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
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
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0
MSSA (*n*=1110)						
Lefamulin	**0.06**	**0.06**	**≤0.008–16**	**NA**	**NA**	**NA**
Azithromycin	0.5	>32	0.03–>32	77.7	1.3	21.0
Ceftaroline	0.25	0.25	≤0.06–0.5	100.0	0.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	97.6	0.3	2.2
Doxycycline	≤0.06	0.12	≤0.06–8	99.7	0.3	0.0
Erythromycin	0.25	>8	≤0.06–>8	77.4	5.9	16.7
Linezolid	1	1	0.25–2	100.0	0.0	0.0
Moxifloxacin	≤0.06	≤0.06	≤0.06–>4	94.5	2.3	3.2
Oxacillin	0.5	0.5	≤0.25–2	100.0	0.0	0.0
Vancomycin	0.5	1	0.25–2	100.0	0.0	0.0
MRSA (*n*=536)						
Lefamulin	**0.06**	**0.12**	**≤0.008–>16**	**NA**	**NA**	**NA**
Azithromycin	>32	>32	0.12–>32	27.2	0.6	72.2
Ceftaroline	1	2	0.25–>8	88.8	10.6	0.6
Clindamycin	≤0.25	>2	≤0.25–>2	65.9	0.0	34.1
Doxycycline	≤0.06	1	≤0.06–>8	95.0	4.9	0.2
Erythromycin	>8	>8	≤0.06–>8	26.7	4.7	68.7
Linezolid	1	1	≤0.12–2	100.0	0.0	0.0
Moxifloxacin	2	>4	≤0.06–>4	29.7	18.5	51.9
Oxacillin	>2	>2	>2–>2	0.0	0.0	100.0
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.

- Viridans group streptococcal isolates were inhibited by lefamulin ($MIC_{50/90}$: *Streptococcus anginosus* group, 0.06/0.25 µg/mL; *Streptococcus bovis* group, 1/2 µg/mL; *Streptococcus mitis* group, 0.12/0.5 µg/mL; *Streptococcus salivarius* group, 0.06/0.12 µg/mL; **Table 3**)
- Among the viridans group streptococcal isolates, high susceptibility rates were seen for vancomycin (100%), ceftriaxone (96.0%), and levofloxacin (93.8%), whereas moderate rates of resistance were observed for erythromycin (34.5%) and clindamycin (9.6%), and 23.8% were nonsusceptible to penicillin

Table 2. Activity of Lefamulin and Comparator Agents Against ß-Hemolytic Streptococci

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Coagulase-negative staphylococci[b] (*n*=276)						
Lefamulin	**0.03**	**0.06**	**≤0.008–>16**	**NA**	**NA**	**NA**
Azithromycin	32	>32	0.03–>32	37.3	0.4	62.3
Ceftaroline	0.25	1	≤0.06–2	–	–	–
Clindamycin	≤0.25	>2	≤0.25–>2	70.3	0.7	29.0
Doxycycline	0.25	1	≤0.06–>8	96.0	2.9	1.1
Erythromycin	>8	>8	≤0.06–>8	37.0	2.2	60.9
Linezolid	0.5	1	≤0.12–>8	98.6	0.0	1.4
Moxifloxacin	0.5	>4	≤0.06–>4	53.3	10.1	36.6
Oxacillin	>2	>2	≤0.25–>2	27.2	0.0	72.8
Vancomycin	1	2	0.25–4	100.0	0.0	0.0
ß-hemolytic streptococci[c] (*n*=389)						
Lefamulin	**0.03**	**0.03**	**≤0.008–16**	**NA**	**NA**	**NA**
Ceftriaxone	0.03	0.06	≤0.015–0.25	100.0	0.0	0.0
Clindamycin	≤0.25	>2	≤0.25–>2	85.3	1.0	13.6
Erythromycin	0.03	>32	≤0.015–>32	74.0	1.0	25.0
Levofloxacin	0.5	1	0.12–>4	97.2	0.5	2.3
Linezolid	1	1	0.5–2	100.0	0.0	0.0
Moxifloxacin	0.12	0.25	≤0.03–>4	–	–	–
Penicillin	0.015	0.06	≤0.004–0.06	100.0	0.0	0.0
Vancomycin	0.25	0.5	0.12–1	100.0	0.0	0.0
***Streptococcus pyogenes* (*n*=165)**						
Lefamulin	**0.015**	**0.03**	**≤0.008–0.03**	**NA**	**NA**	**NA**
Ceftriaxone	0.03	0.03	≤0.015–0.06	100.0	0.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	95.8	0.0	4.2
Erythromycin	0.03	1	≤0.015–>32	87.8	1.2	11.0
Levofloxacin	0.5	1	0.12–2	100.0	0.0	0.0
Linezolid	1	1	0.5–2	100.0	0.0	0.0
Moxifloxacin	0.12	0.25	≤0.03–4	–	–	–
Penicillin	0.008	0.015	≤0.004–0.06	100.0	0.0	0.0
Vancomycin	0.25	0.5	0.12–0.5	100.0	0.0	0.0
***Streptococcus agalactiae* (*n*=168)**						
Lefamulin	**0.03**	**0.03**	**≤0.008–16**	**NA**	**NA**	**NA**
Ceftriaxone	0.06	0.06	0.03–0.25	100.0	0.0	0.0
Clindamycin	≤0.25	>2	≤0.25–>2	76.2	1.8	22.0
Erythromycin	0.06	>32	0.03–>32	64.3	1.2	34.5
Levofloxacin	1	1	0.25–>4	94.6	0.6	4.8
Linezolid	1	2	0.5–2	100.0	0.0	0.0
Moxifloxacin	0.12	0.25	0.06–>4	–	–	–
Penicillin	0.03	0.06	0.008–0.06	100.0	0.0	0.0
Vancomycin	0.5	0.5	0.25–1	100.0	0.0	0.0

I=intermediate; NA=not applicable; R=resistant; S=susceptible.
[a]Criteria as published by CLSI 2018.
[b]Organisms include *Staphylococcus auricularis* (1), *S. capitis* (26), *S. caprae* (2), *S. cohnii* (1), *S. epidermidis* (152), *S. haemolyticus* (40), *S. hominis* (28), *S. lugdunensis* (11), *S. pettenkoferi* (3), *S. saprophyticus* (2), *S. schleiferi* (1), *S. sciuri* (2), *S. simulans* (1), and *S. warneri* (6).
[c]Organisms include *Streptococcus agalactiae* (168), *S. dysgalactiae* (56), and *S. pyogenes* (165).

Table 3. Activity of Lefamulin and Comparator Agents Against Viridans Group Streptococci

Antibacterial Agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***Streptococcus anginosus* group[b] (*n*=44)**						
Lefamulin	**0.06**	**0.25**	**≤0.008–0.5**	**NA**	**NA**	**NA**
Ceftriaxone	0.25	0.25	≤0.015–0.5	100.0	0.0	0.0
Clindamycin	≤0.25	>2	≤0.25–>2	86.4	0.0	13.6
Erythromycin	≤0.015	2	≤0.015–>32	75.0	6.8	18.2
Levofloxacin	0.5	1	0.25–2	100.0	0.0	0.0
Moxifloxacin	0.12	0.25	≤0.03–0.5	–	–	–
Penicillin	0.03	0.06	≤0.004–0.12	100.0	0.0	0.0
Vancomycin	0.5	1	≤0.06–1	100.0	0.0	0.0
***Streptococcus bovis* group[c] (*n*=45)**						
Lefamulin	**1**	**2**	**≤0.008–>16**	**NA**	**NA**	**NA**
Ceftriaxone	0.12	0.12	0.03–0.25	100.0	0.0	0.0
Clindamycin	≤0.25	>2	≤0.25–>2	82.2	2.2	15.6
Erythromycin	0.03	>32	≤0.015–>32	64.4	0.0	35.6
Levofloxacin	1	4	0.5–>4	86.7	4.4	8.9
Moxifloxacin	0.25	4	0.12–>4	–	–	–
Penicillin	0.06	0.06	0.015–0.12	100.0	0.0	0.0
Vancomycin	0.25	0.5	0.25–0.5	100.0	0.0	0.0
***Streptococcus mitis* group[d] (*n*=48)**						
Lefamulin	**0.12**	**0.5**	**0.015–0.5**	**NA**	**NA**	**NA**
Ceftriaxone	0.12	2	≤0.015–>2	89.6	6.2	4.2
Clindamycin	≤0.25	≤0.25	≤0.25–>2	91.7	2.1	6.2
Erythromycin	0.03	4	≤0.015–>32	54.2	0.0	45.8
Levofloxacin	1	2	0.5–>4	91.7	4.2	4.2
Moxifloxacin	0.12	0.25	≤0.03–4	–	–	–
Penicillin	0.12	1	0.008–4	50.0	43.8	6.2
Vancomycin	0.5	0.5	0.25–0.5	100.0	0.0	0.0
***Streptococcus salivarius* group[e] (*n*=40)**						
Lefamulin	**0.06**	**0.12**	**≤0.008–0.25**	**NA**	**NA**	**NA**
Ceftriaxone	0.12	0.5	≤0.015–2	95.0	5.0	0.0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	97.5	0.0	2.5
Erythromycin	≤0.015	4	≤0.015–>32	62.5	0.0	37.5
Levofloxacin	1	1	0.25–>4	97.5	0.0	2.5
Moxifloxacin	0.12	0.25	≤0.03–2	–	–	–
Penicillin	0.12	0.5	0.008–4	55.0	42.5	2.5
Vancomycin	0.5	0.5	0.25–1	100.0	0.0	0.0

I=intermediate; NA=not applicable; R=resistant; S=susceptible.
[a]Criteria as published by CLSI 2018.
[b]Organisms include *Streptococcus anginosus* (24), *S. anginosus* group (10), *S. constellatus* (5), and *S. intermedius* (5).
[c]Organisms include *Streptococcus bovis* group (3), *S. equinus* (2), *S. gallolyticus* (33), and *S. lutetiensis* (7).
[d]Organisms include *Streptococcus gordonii* (2), *S. mitis* group (32), *S. mitis/oralis* (3), *S. oralis* (1), *S. parasanguinis* (7), and *S. sanguinis* (3).
[e]Organisms include *Streptococcus salivarius* (12), *S. salivarius* group (11), *S. salivarius/vestibularis* (12), and *S. vestibularis* (5).

CONCLUSIONS

- Lefamulin demonstrated potent *in vitro* activity against pathogens commonly causing ABSSSI and BSI in this contemporary collection of isolates
- The activity of lefamulin was not affected by resistance to other classes of antibiotics
- These data support the continued development of lefamulin for the treatment of ABSSSI and further exploration of lefamulin activity in BSI

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Disclosures

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