P1823

In Vitro Activity of Lefamulin Against Contemporary *Staphylococcus aureus* Isolates From Patients in Europe (SENTRY 2016)

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INTRODUCTION & PURPOSE

- Lefamulin is under clinical development as the first semisynthetic pleuromutilin antibiotic for intravenous (IV) and oral treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in humans
- Lefamulin inhibits protein synthesis by interacting selectively and specifically with the A- and P-sites in the peptidyl transferase center of the 50S ribosomal subunit, thereby triggering tight binding via an induced fit mechanism[1]
- Previous reports show that lefamulin is active *in vitro* against CABP- and ABSSSI-causing pathogens (*Staphylococcus aureus*, coagulase-negative staphylococci [CoNS], β-hemolytic streptococci, viridans group streptococci, *Enterococcus faecium, Mycoplasma pneumoniae, Streptococcus pneumoniae, Haemophilus influenzae*, and *Moraxella catarrhalis*) and its activity is not influenced by resistance to other antibacterial classes[2-5]
  - In the phase 2 study treating ABSSSI, the efficacy of lefamulin was comparable to vancomycin against Gram-positive pathogens, including *S. aureus*; lefamulin was equally effective against infections caused by methicillin-susceptible *S. aureus* (MSSA) and methicillin-resistant *S. aureus* (MRSA)[6]
  - A recent phase 3 trial for the treatment of CABP showed that lefamulin (150 mg IV every 12 hours [q12h] or 600 mg orally [PO] q12h for 7 days) was noninferior to moxifloxacin ± linezolid (400 mg IV every 24 hours [q24h] or 400 mg PO q24h for 7 days; if MRSA was suspected, linezolid was added at 600 mg q12h IV or PO)
- *S. aureus* can cause a range of illnesses and is a leading cause of skin and soft tissue infections, endocarditis, CABP, and bloodstream infections (BSIs)[7]
- The objective of this study was to investigate the activity of lefamulin and comparators against a contemporary collection of *S. aureus* isolates from Europe in 2016

METHODS

- 550 unique *S. aureus* isolates were collected from hospitalized patients with BSI (*n*=275), ABSSSI (*n*=165), or pneumonia (*n*=110) in 19 countries at 37 sites in 2016 as part of the SENTRY Surveillance Program
- Susceptibility testing was done using Clinical and Laboratory Standards Institute (CLSI) broth microdilution and was interpreted with the European Committee on Antimicrobial Susceptibility Testing (EUCAST) 2017 breakpoint criteria
- Quality-control organisms as suggested by CLSI were tested concurrently as controls

RESULTS

- Lefamulin was one of the most potent compounds tested, with 99.6% of all *S. aureus* isolates inhibited at a concentration ≤0.25 mg/L (*n*=550; $MIC_{50/90}$ values of 0.06/0.12 mg/L; **Table 1** and **Figure 1**)
  - Susceptibility rates for *S. aureus* (*n*=550) were >90% for clindamycin ($MIC_{50/90}$, ≤0.25/≤0.25 mg/L), doxycycline ($MIC_{50/90}$, ≤0.06/0.25 mg/L), tigecycline ($MIC_{50/90}$, ≤0.06/0.12 mg/L), vancomycin ($MIC_{50/90}$, 0.5/1 mg/L), linezolid ($MIC_{50/90}$, 1/1 mg/L), and ceftaroline ($MIC_{50/90}$, 0.25/1 mg/L)
  - 2 *S. aureus* isolates displayed lefamulin MIC values of 1 mg/L and >16 mg/L; 1 isolate (MSSA) was from a patient with BSI in France and the other (MRSA) was from a patient with pneumonia in Germany, respectively. Both isolates were susceptible to linezolid. The putative efflux pumps *vga*(A) and *vga*(E) were identified as resistance determinants
- Lefamulin's activity was not influenced by resistance to other antibiotic classes **(Table 2)**
  - Lefamulin was active *in vitro* against MRSA (*n*=155), erythromycin-resistant (eryR) *S. aureus* (*n*=143), and multidrug-resistant (MDR) *S. aureus* (*n*=65; $MIC_{50/90}$ for all groups, 0.06/0.12 mg/L)
  - MRSA isolates demonstrated high resistance rates to azithromycin (55.0%), clindamycin (21.3%), erythromycin (52.9%), levofloxacin (71.0%), and moxifloxacin (71.0%)

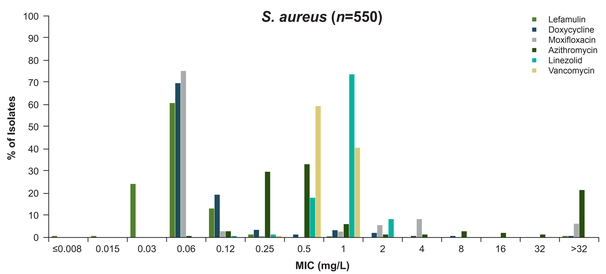
RESULTS (continued)

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

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
***S. aureus* (*n*=550)**						
Lefamulin	**0.06**	**0.12**	**≤0.008–>16**	**NA**	**NA**	**NA**
Azithromycin	0.5	>32	0.06–>32	71.1	0.9	28.0
Ceftaroline	0.25	1	≤0.06–2	98.0	2.0	0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	93.1	0.2	6.7
Doxycycline	≤0.06	0.25	≤0.06–>8	96.5	2.0	1.5
Erythromycin	0.25	>8	≤0.06–>8	72.2	1.8	26.0
Levofloxacin	0.25	>4	≤0.03–>4	77.6	–	22.4
Linezolid	1	1	≤0.12–2	100	–	0
Moxifloxacin	≤0.06	4	≤0.06–>4	77.8	–	22.2
Oxacillin	0.5	>2	≤0.25–>2	71.8	–	28.2
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	99.8	0	0.2
Vancomycin	0.5	1	0.25–1	100	–	0
MSSA (*n*=395)						
Lefamulin	**0.06**	**0.06**	**≤0.008–1**	**NA**	**NA**	**NA**
Azithromycin	0.5	>32	0.06–>32	82.0	0.8	17.2
Ceftaroline	0.25	0.25	≤0.06–0.5	100	0	0
Clindamycin	≤0.25	≤0.25	≤0.25–>2	98.7	0.3	1.0
Doxycycline	≤0.06	0.12	≤0.06–4	98.0	1.3	0.8
Erythromycin	0.12	>8	≤0.06–>8	83.3	1.3	15.4
Levofloxacin	0.25	0.25	≤0.03–>4	96.7	–	3.3
Linezolid	1	1	0.25–2	100	–	0
Moxifloxacin	≤0.06	≤0.06	≤0.06–4	97.0	–	3.0
Oxacillin	0.5	1	≤0.25–2	100	–	0
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–2	100	0	0
Vancomycin	0.5	1	0.25–1	100	–	0

EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MSSA=methicillin-susceptible *Staphylococcus aureus*; NA=not applicable; R=resistant; S=susceptible.
*Criteria as published by EUCAST (2017).

Figure 1. MIC Distributions for Lefamulin and Comparators



MIC=minimum inhibitory concentration.

RESULTS (continued)

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

Antimicrobial Agent	mg/L			EUCAST*		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
MRSA (*n*=155)						
Lefamulin	**0.06**	**0.12**	**≤0.008–>16**	**NA**	**NA**	**NA**
Azithromycin	16	>32	0.12–>32	43.2	1.3	55.5
Ceftaroline	1	1	0.25–2	92.9	7.1	0
Clindamycin	≤0.25	>2	≤0.25–>2	78.7	0	21.3
Doxycycline	≤0.06	1	≤0.06–>8	92.9	3.9	3.2
Erythromycin	4	>8	≤0.06–>8	43.9	3.2	52.9
Levofloxacin	>4	>4	0.12–>4	29.0	–	71.0
Linezolid	1	1	≤0.12–2	100	–	0
Moxifloxacin	2	>4	≤0.06–>4	29.0	–	71.0
Oxacillin	>2	>2	>2–>2	0	–	100
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	99.4	0	0.6
Vancomycin	0.5	1	0.25–1	100	–	0
eryR *S. aureus* (*n*=143)						
Lefamulin	**0.06**	**0.12**	**0.015–>16**	**NA**	**NA**	**NA**
Azithromycin	>32	>32	2–>32	0	0.7	99.3
Ceftaroline	0.5	1	0.12–2	95.1	4.9	0
Clindamycin	≤0.25	>2	≤0.25–>2	74.1	0	25.9
Doxycycline	≤0.06	1	≤0.06–>8	93.7	4.2	2.1
Erythromycin	>8	>8	4–>8	0	0	100
Levofloxacin	0.5	>4	0.06–>4	52.4	–	47.6
Linezolid	1	1	0.25–2	100	–	0
Moxifloxacin	0.12	>4	≤0.06–>4	52.4	–	47.6
Oxacillin	>2	>2	≤0.25–>2	42.7	–	57.3
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	99.3	0	0.7
Vancomycin	0.5	1	0.25–1	100	–	0
MDR *S. aureus* (*n*=65)						
Lefamulin	**0.06**	**0.12**	**0.03–0.25**	**NA**	**NA**	**NA**
Azithromycin	>32	>32	2–>32	0	1.5	98.5
Ceftaroline	1	2	0.5–2	89.2	10.8	0
Clindamycin	≤0.25	>2	≤0.25–>2	52.3	0	47.7
Doxycycline	≤0.06	0.5	≤0.06–8	95.4	1.5	3.1
Erythromycin	>8	>8	4–>8	0	0	100
Levofloxacin	>4	>4	4–>4	0	–	100
Linezolid	1	1	0.25–2	100	–	0
Moxifloxacin	4	>4	1–>4	0	–	100
Oxacillin	>2	>2	>2–>2	0	–	100
Trimethoprim-sulfamethoxazole	≤0.5	≤0.5	≤0.5–>4	98.5	0	1.5
Vancomycin	0.5	1	0.25–1	100	–	0

eryR=erythromycin resistant (EUCAST 2017); EUCAST=European Committee on Antimicrobial Susceptibility Testing; I=intermediate; MDR=multidrug resistant, defined as erythromycin-R (EUCAST 2017) oxacillin-R (EUCAST 2017) and moxifloxacin-R (EUCAST 2017) *Staphylococcus aureus*; MRSA=methicillin-resistant *Staphylococcus aureus*; NA=not applicable; R=resistant; S=susceptible.
*Criteria as published by EUCAST (2017).

CONCLUSIONS

- Lefamulin demonstrated potent activity against this contemporary collection of *S. aureus* isolates from Europe from patients with BSI, ABSSSI, and pneumonia
- The *in vitro* activity of lefamulin against *S. aureus* was not influenced by resistance to other antimicrobial classes
- This study supports the continued development of lefamulin as an empiric treatment for CABP and ABSSSI

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