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In Vitro Antibacterial Activity of Lefamulin against *S. aureus* Collected from Hospitalized Patients with Bacterial Pneumonia in US

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ABSTRACT (amended)

Background: Lefamulin is the first semi-synthetic pleuromutilin antibiotic for IV and oral use in humans and is currently in Phase 3 trials for the treatment of CABP in adults. Lefamulin effectively and selectively inhibits bacterial translation by binding to the A- and P-site of the peptidyl transferase center (PTC) via an induced fit mechanism whereby nucleotides in the PTC shift and tighten the binding pocket around lefamulin. [1,2] This study investigated the susceptibility of *S. aureus* strains collected from patients hospitalized with pneumonia in the US in 2015 to lefamulin and comparators.

Methods: A total of 506 unique *S. aureus* isolates were collected from hospitalized patients with pneumonia in the US (58 sites) in 2015 as part of the SENTRY surveillance program. Susceptibility testing was conducted using the CLSI broth microdilution method, and susceptibility was interpreted per CLSI (2016) breakpoint criteria. [3] Only one isolate per patient infection episode was included in surveillance.

Results: Lefamulin was the most potent compound tested with 99.4% of all isolates inhibited at concentrations ≤0.12 µg/mL ($MIC_{50/90}$ values of 0.06/0.12 mg/L). A total of 36.8% of isolates were oxacillin-resistant (MRSA) and they also exhibited lefamulin $MIC_{50/90}$ of 0.06/0.12 mg/L. Susceptibility rates among *S. aureus* including MRSA were 97.8-100% for ceftaroline, vancomycin, and linezolid, whereas only 45.7% and 66.6% were susceptible (S) to azithromycin and levofloxacin, respectively. MRSA strains showed limited susceptibility to azithromycin (85.5% resistant), levofloxacin (73.1% resistant) and clindamycin (41.4% resistant).

Conclusion: Lefamulin demonstrated potent *in vitro* activity against *S. aureus* strains collected from patients hospitalized in the US with pneumonia regardless of susceptibility phenotype to the other antibiotics tested. These data and lefamulin's activity against other typical and atypical respiratory pathogens support further development of lefamulin for the treatment of CABP, including in those with severe disease.

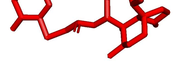

Figure 1. Lefamulin

INTRODUCTION

S. aureus is a well-recognized cause of pneumonia from both the community and hospital setting.[4] The clinical management of staphylococcal pneumonia is complicated by the high prevalence of methicillin-resistance observed in *S. aureus* (MRSA) and the invasive infection it causes.[5]

Lefamulin is the first representative of pleuromutilin class in clinical development for systemic administration. Pleuromutilins inhibit bacterial protein synthesis of Gram-positive and Gram-negative organisms, as well as atypical respiratory pathogens. [6,7] 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." Phase 1 and 2 trials have demonstrated that IV and oral administration of lefamulin are well tolerated. Furthermore, lefamulin (100mg 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. [8] Currently lefamulin is in late stage development for the treatment of community-acquired bacterial pneumonia (CABP).

RESULTS

- Lefamulin showed potent antibacterial activity against *S. aureus* isolates including resistant isolates (Table 1, Figure 2).

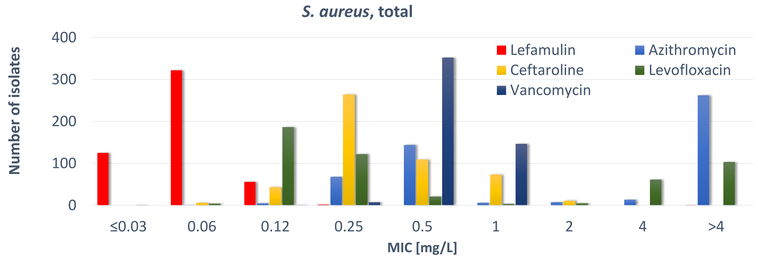

Figure 2. MIC distributions of lefamulin and comparators

Table 1. *In vitro* activity of lefamulin and comparators [mg/L]

Organism (*N*)	MIC_{50}	MIC_{90}	MIC_{99}	Range [mg/L]	% S [a]	% I [a]	% R [a]
***S. aureus* (506)**							
Lefamulin	0.06	0.12	0.12	≤0.03 to >1 [b]	-	-	-
Azithromycin	>4	>4	>4	0.06 to >4	45.7	2.6	**51.8**
Ceftaroline	0.25	1	2	≤0.06 to 2	97.8	2.2	0.0
Clindamycin	≤0.25	>2	>2	≤0.25 to >2	80.2	0.2	**19.6**
Doxycycline	≤0.06	0.12	4	≤0.06 to 8	99.4	0.6	0.0
Erythromycin	4	>8	>8	0.12 to >8	44.7	7.5	**47.8**
Levofloxacin	0.25	>4	>4	≤0.03 to >4	66.6	1.0	**32.4**
Linezolid	1	1	2	0.25 to 2	100.0	-	0.0
Oxacillin	0.5	>2	2	≤0.25 to >2	63.2	-	**36.8**
Vancomycin	0.5	1	1	≤0.12 to 1	100.0	0.0	0.0
MRSA (186)							
Lefamulin	0.06	0.12	0.25	≤0.03 to >1	-	-	-
Azithromycin	>4	>4	>4	0.12 to >4	13.4	1.1	**85.5**
Ceftaroline	0.5	1	2	0.5 to 2	94.1	5.9	0.0
Clindamycin	≤0.25	>2	>2	≤0.25 to >2	58.6	0.0	**41.4**
Doxycycline	≤0.06	0.5	4	≤0.06 to 8	99.5	0.5	0.0
Erythromycin	>8	>8	>8	0.12 to >8	12.9	5.4	**81.7**
Levofloxacin	4	>4	>4	0.12 to >4	26.3	0.5	**73.1**
Linezolid	1	1	2	0.25 to 2	100.0	-	0.0
Oxacillin	>2	>2	>2	>2 to >2	0.0	-	**100.0**
Vancomycin	0.5	1	1	0.25 to 1	100.0	0.0	0.0

[a], Criteria as published by CLSI [2017]; [b], One of 506 isolates showed a lefamulin MIC of >1 mg/L.

- Lefamulin was the most potent compound tested with all isolates except one single strain (99.8%) inhibited at a lefamulin concentration of ≤0.25 mg/L ($MIC_{50/90}$ values of 0.06/0.12 mg/L).
- The lefamulin activity was not affected by resistance to other antibiotics tested including macrolides, tetracyclines, fluoroquinolones, or ß-lactam antibiotics or their nosocomial status.
  - 38.6% of isolates were MRSA, of which were n=79 community-acquired (CA-MRSA) and n=32 nosocomial (HA-MRSA)
  - Lefamulin MIC distributions were similar between subsets including MSSA vs. MRSA and community-acquired vs. nosocomial isolates
  - MSSA showed lefamulin $MIC_{50/90}$ of 0.06/0.12 mg/L and MRSA 0.12/0.12 mg/L
  - CA-SA (n=204; MSSA and MRSA) displayed a lefamulin $MIC_{50/90}$ of 0.06/0.12 mg/L and HA-SA (n=82) $MIC_{50/90}$ of 0.06/0.06 mg/L
- *S. aureus* isolates were largely susceptible to doxycycline (99.4%), ceftaroline (97.8%), linezolid (100%) and vancomycin (100%)
- Susceptiblity to macrolides, fluoroquinolones and lincosamides was significantly reduced, particularly among MRSA
  - 85.5% of MRSA and 32.2% of MSSA were resistant to azithromycin
  - 73.1% of MRSA and 8.8% of MSSA were resistant to levofloxacin
  - 41.4% of MRSA and 6.9% of MSSA were resistant to clindamycin

CONCLUSIONS

- **Lefamulin displayed potent *in vitro* activity against this contemporary collection of *S. aureus* isolates collected from hospitalized patients with pneumonia**
- **Lefamulin was the most active compound against MRSA and MSSA including both, community-acquired and nosocomial isolates, irrespective of the resistance phenotype to other antibiotic classes including macrolides, fluoroquinolones, or tetracyclines or ß-lactam antibiotics.**
- **These data support the development of lefamulin for infections caused by *S. aureus*, including CAP, HAP and acute bacterial skin and skin structure infections (ABSSSI).**

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