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Lefamulin Activity against Bacterial Pathogens Typically Causing Pneumonia Collected from European Medical Centers in 2020 and 2021

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INTRODUCTION

- Lefamulin is a novel first-in-class pleuromutilin antibiotic approved in the United States (US), Europe (EU), and Canada for the oral and intravenous treatment of community-acquired pneumonia (CAP) in adults caused by susceptible typical and atypical bacterial organisms, including *S. aureus*.
- CAP is the most common infection-related cause of death in Europe, with an incidence of 1.7 to 11.6 cases per 1000 person-years.[1]
- *Streptococcus pneumoniae* is the most frequently isolated bacterial pathogen from patients with CAP, with prevalences that vary by geographic region. Other bacterial causes of CAP include *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*, as well as atypical pathogens.[1,2]
- Increasing resistance rates and safety concerns around available antibiotics have created the need for new CAP treatment options.[2,3]
- Lefamulin is a novel pleuromutilin protein synthesis inhibitor with a unique mode-of-action, low potential for resistance development and has demonstrated potent clinical efficacy in global phase 3 clinical trials in CAP patients with moderate to severe pneumonia with a good safety and tolerability profile.[4-8]
- This study evaluated the *in vitro* activity of lefamulin and susceptibility of comparator antibiotics used to treat CAP against contemporary isolates from bacterial species responsible for CAP collected in European medical centers in 2020–2021.

MATERIALS AND METHODS

Bacterial isolates

- Overall, 3,345 organisms were collected within the SENTRY Surveillance Program from 35 medical centers from the following countries:
  - Belgium
  - Czech Republic
  - France
  - Germany
  - Greece
  - Hungary
  - Ireland
  - Israel
  - Italy
  - Poland
  - Portugal
  - Romania
  - Slovenia
  - Spain
  - Sweden
  - Switzerland
  - Turkey
  - United Kingdom
- Isolates were from infections of the respiratory tract (44.8%), skin and soft tissue (28.9%), bloodstream (18.0%), and other sites (8.3%).
- Organisms were susceptibility tested by CLSI reference broth microdilution methods and EUCAST breakpoints were applied when available.[9,10]

RESULTS

- Lefamulin demonstrated potent antibacterial activity against all tested CAP pathogens and was unaffected by resistance to other antibacterial classes.
- *Streptococcus pneumoniae* (728)
  - 100% of *S. pneumoniae* isolates were inhibited at lefamulin concentrations at or below the susceptible EUCAST and CLSI breakpoints of ≤0.5 mg/L; lefamulin displayed $MIC_{50/90}$ values of 0.12/0.25 mg/L (Table 1 and Figure 1).
  - Lefamulin activity against *S. pneumoniae* was not adversely affected by resistance to other antimicrobials and lefamulin remained fully active ($MIC_{50/90}$ of 0.06/0.12 mg/L) against resistant subsets including macrolide-, doxycycline- and penicillin-resistant isolates (Table 1 and Figure 1).
  - The susceptibility rates of other antibacterials that are commonly used to treat CAP were lower: azithromycin (77.7%S), doxycycline (82.9%S), amoxicillin-clavulanic acid (82.7%S) and moxifloxacin (99.7%S) (Table 1).
- *Staphylococcus aureus* including MRSA (1,829)
  - Lefamulin was also highly active against *S. aureus*, demonstrating an $MIC_{50/90}$ of 0.06/0.12 mg/L and 99.6% susceptibility per EUCAST, CLSI, and US FDA criteria (Table 1 and Figure 2).
  - Lefamulin remained highly active against MRSA (15.5% of *S. aureus* isolates; $MIC_{50/90}$ of 0.06/0.12 mg/L), azithromycin-resistant ($MIC_{50/90}$ of 0.06/0.12 mg/L), and moxifloxacin-resistant isolates ($MIC_{50/90}$ of 0.06/0.25 mg/L) (Table 1 and Figure 2).
- *Haemophilus influenzae* and *H. parainfluenzae*
  - Lefamulin was active against *H. influenzae* (99.6% susceptible when applying the US FDA and CLSI susceptible breakpoint of ≤2 mg/L), including β-lactamase-positive strains (Table 1).
  - Against *H. parainfluenzae* lefamulin $MIC_{50/90}$ were 2/4 mg/L and all isolates were inhibited at lefamulin concentrations of ≤4 mg/L.
- β-hemolytic and viridans group *Streptococcus* spp.
  - Potent lefamulin activity was determined against β-hemolytic and viridans group streptococci with complete inhibition of isolates at lefamulin concentrations ≤0.5 mg/L, the EUCAST and CLSI breakpoint for *S. pneumoniae*: *S. agalactiae* (lefamulin $MIC_{50/90}$ of 0.03/0.06 mg/L), *S. pyogenes* (lefamulin $MIC_{50/90}$ of 0.03/0.03 mg/L), and viridans group streptococci (lefamulin $MIC_{50/90}$ of 0.12/0.25 mg/L; Table 1).

Table 1. Antimicrobial susceptibility of bacterial pathogens typically causing pneumonia collected from European medical centers (2020 and 2021)

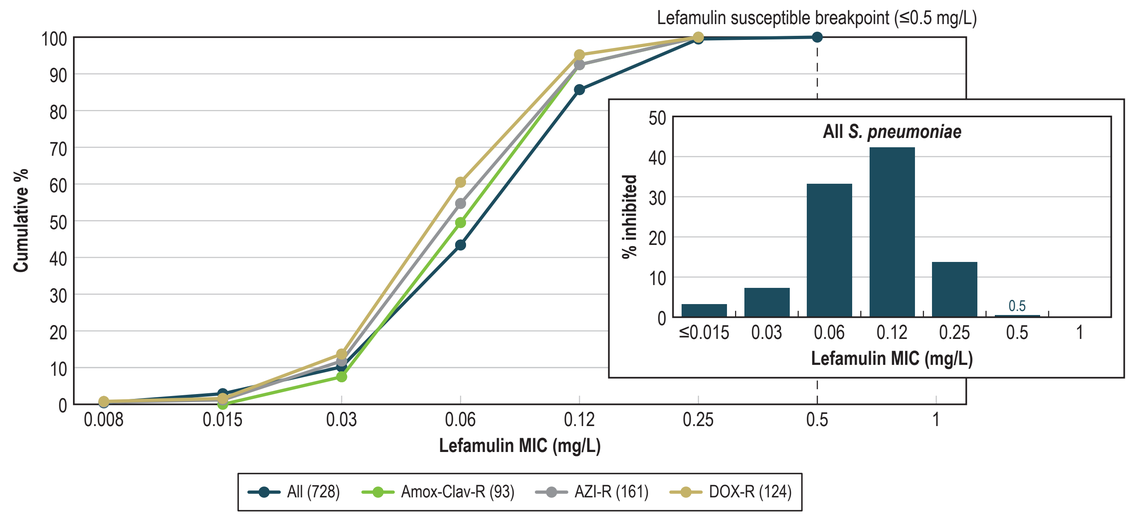
Organism / Resistant subset (no.)	$MIC_{50/90}$ [mg/L] (% Susceptible per EUCAST)				
	Lefamulin	Amox-Clav	Azithromycin	Moxifloxacin	Doxy/Tetra[a]
S. pneumoniae (728)	0.12/0.25 (100.0)	≤0.03/2 (82.7)	0.06/>4 (77.7)	0.12/0.25 (99.7)	0.12/>1 (82.9)
Penicillin-R (43)	0.06/0.12 (100.0)	>4/>4 (0.0)	>4/>4 (34.9)	0.12/0.25 (97.7)	0.12/>1 (60.5)
Azithromycin-R (161)	0.06/0.12 (100.0)	1/4 (49.7)	>4/>4 (0.0)	0.12/0.25 (98.8)	>1/>1 (29.8)
Doxycycline-R (124)	0.06/0.12 (100.0)	1/2 (49.2)	>4/>4 (7.3)	0.12/0.12 (98.4)	>1/>1 (0.0)
S. aureus (1,829)	0.06/0.12 (99.6)	Not tested	1/>8 (70.9)	≤0.06/2 (88.3)	≤0.06/0.12 (97.1)
MRSA (283)	0.06/0.12 (98.2)	Not tested	>8/>8 (42.8)	2/>4 (40.6)	≤0.06/1 (91.9)
Azithromycin-R (510)	0.06/0.12 (99.4)	Not tested	>8/>8 (0.0)	≤0.06/>4 (75.6)	≤0.06/0.5 (95.3)
Moxifloxacin-R (214)	0.06/0.25 (98.1)	Not tested	>8/>8 (40.7)	4/>4 (0.0)	≤0.06/0.25 (96.2)
H. influenzae (279)	0.5/1 (99.6)[b]	0.5/2 (95.3)	1/2 (97.1)	0.03/0.06 (97.8)	0.5/0.5 (99.3)
β-lactamase-pos. (48)	0.5/1 (100.0)[b]	1/1 (97.9)	0.5/1 (97.9)	0.03/0.06 (95.8)	0.5/0.5 (95.8)
H. parainfluenzae (24)	2/4 (NA)	0.25/1 (100.0)	1/1 (100.0)	0.06/0.25 (66.7)	0.5/1 (100.0)
M. catarrhalis (164)	0.12/0.12 (100.0)	0.12/0.25 (100.0)	0.03/0.03 (99.4)	0.06/0.06 (100.0)	0.25/0.5 (100.0)
S. agalactiae (128)	0.03/0.06 [100.0][c]	0.06/0.06 (100.0)	0.06/>4 (66.4)	0.12/0.25 [96.9][d]	>1/>1 [21.1][e]
S. pyogenes (100)	0.03/0.03 [100.0][c]	0.03/0.03 (100.0)	0.12/0.25 (91.0)	0.12/0.25 (100.0)	0.12/>1 (72.0)
VGS (93)[f]	0.12/0.25 [100.0][c]	0.12/2 (81.5)	0.06/>4 [55.9][g]	0.12/0.25 [100.0][d]	0.12/>1 [81.7][e]

[a] Doxycycline for *S. aureus* and streptococci, and tetracycline for *Haemophilus* spp. and *M. catarrhalis*.
[b] US FDA and CLSI breakpoint of ≤2 mg/L was applied.
[c] Inhibited at ≤0.5 mg/L (EUCAST breakpoint for *S. pneumoniae*)
[d] Inhibited at ≤0.5 mg/L (EUCAST breakpoint for *S. pneumoniae*)
[e] Inhibited at ≤1 mg/L (EUCAST breakpoint for *S. pneumoniae*)
[f] Viridans group streptococci includes *S. anginosus, S. mitis,* and *S. salivarius* groups.
[g] CLSI breakpoint of ≤0.5 mg/L was applied.
Abbreviations: Amox-Clav, amoxicillin-clavulanate; MRSA, methicillin-resistant *S. aureus*; R, resistant per EUCAST criteria; VGS, viridans group streptococci.

CONCLUSIONS

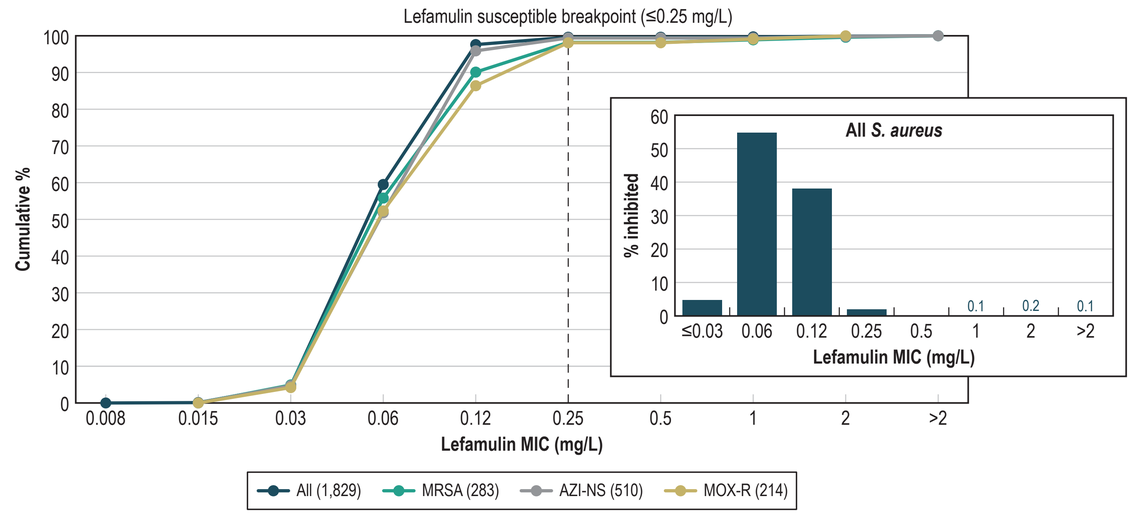
- Lefamulin displayed potent *in vitro* activity against this contemporary collection of CAP pathogens from Europe.
- Lefamulin activity was unaffected by resistance to other antibiotic classes and particularly those commonly used to treat CAP, including fluoroquinolones, macrolides, β-lactams, and tetracyclines.
- Lefamulin represents a valuable empiric treatment option for ambulatory and hospitalized patients with CAP irrespective of the current resistance rates in the respective regions, countries or institutions.

Figure 1. Lefamulin activity (cumulative MIC distributions) against *S. pneumoniae* and resistant subsets (2020–2021)



Abbreviations: Amox-Clav, amoxicillin-clavulanate; R, resistant per EUCAST criteria; AZI, azithromycin; DOX, doxycycline.

Figure 2. Antimicrobial susceptibility of *S. aureus* and resistant subsets (2020–2021)



Abbreviations: MRSA, methicillin-resistant *S. aureus*; AZI, azithromycin; MOX, moxifloxacin; R, resistant per EUCAST criteria.

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