IDWEEK 2021

In Vitro Activity of Lefamulin against *Staphylococcus aureus* Isolated from the Lower Respiratory Tract of Children with Cystic Fibrosis

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INTRODUCTION

- *Staphylococcus aureus* is the most isolated organism in cystic fibrosis (CF) patients and the primary cause of recurrent acute pulmonary infection and progressive decline in lung function.
- Antimicrobial treatment is recommended for symptomatic CF patients with persistent detection of *S. aureus*, but the best antibiotic approach has yet to be established.
  - Current treatments most often include oral trimethoprim-sulfamethoxazole or linezolid for outpatients, while for inpatients IV linezolid or IV vancomycin are commonly used. Tetracyclines, fusidic acid, and ceftaroline have also been described as alternative treatment options.
  - All current options have shortcomings including an absence of evidence-based guidance for an effective dosage in CF patients, adverse effects, or a high rate of resistance.
- Lefamulin (Xenleta®) is the first oral and IV pleuromutilin antibiotic approved by the US Food and Drug Administration (US FDA) for the treatment of community-acquired bacterial pneumonia (CABP) and is approved in Europe and Canada.
  - Lefamulin is a first-in-class, semi-synthetic pleuromutilin that inhibits bacterial protein synthesis by binding to the 50S ribosomal subunit at the A- and P- sites in the peptidyl transferase center (PTC) via an “induced-fit” mechanism, which prohibits the correct positioning of the tRNA.
  - Lefamulin has a targeted spectrum of activity against key respiratory CABP pathogens, including isolates resistant to standard-of-care therapies.
  - Administration to children is currently being evaluated according to the pediatric investigation plan. A phase 1 clinical study in CF is planned to start in the second half of 2021.
- We evaluated the *in vitro* activity of lefamulin against *S. aureus* respiratory isolates from pediatric CF patients.

MATERIALS AND METHODS

- A total of 224 unique *S. aureus* isolates (1/patient) were collected from the lower respiratory tract of children (≤17 years old) with CF and pulmonary exacerbation.
- Organisms were from qualified respiratory specimens and determined to be the probable cause of pulmonary exacerbation by the participant center.
- The isolates were collected in 2018–2020 from 22 medical centers in 11 countries. Most isolates were from the US (43.3%), Spain (24.1%), France (20.5%), and Costa Rica (7.1%).
- Susceptibility testing was performed by CLSI reference broth microdilution methods by JMI Laboratories.

RESULTS

- Lefamulin was highly active against the CF *S. aureus* collection ($MIC_{50/90}$, 0.06/0.12 mg/L), with 99.6% of isolates inhibited at ≤0.25 mg/L, consistent with the susceptible breakpoints published by the US FDA, CLSI, and EUCAST (Table 1).
  - Only 1 lefamulin-non-susceptible isolate (MIC, 1 mg/L) was observed, a methicillin-susceptible (MSSA) collected in Costa Rica in 2018 that carried a *vga*(A) gene.
- Lefamulin retained potent activity against resistant *S. aureus* isolates as well as those isolates with multiple resistance phenotypes (Table 2, Figures 1 and 2).
  - methicillin-resistant *S. aureus* (MRSA, $MIC_{50/90}$, 0.06/0.12 mg/L)
  - azithromycin-resistant (n=115; $MIC_{50/90}$, 0.06/0.12 mg/L)
  - levofloxacin-resistant (n=23; $MIC_{50/90}$, 0.06/0.12 mg/L)
  - clindamycin-resistant (n=11; $MIC_{50/90}$, 0.06/0.12 mg/L)
  - gentamicin-resistant (n=9; MIC range of 0.03–0.12 mg/L)
  - 5 multidrug-resistant isolates that were resistant to oxacillin, erythromycin, clindamycin, and gentamicin per CLSI criteria were inhibited by lefamulin concentrations of 0.03–0.06 mg/L (data not shown).
- Against MRSA, susceptibility to azithromycin was 23.5% and levofloxacin was 64.7% (Table 2).
- All isolates were susceptible to vancomycin, linezolid, and ceftaroline (Table 1).
- Among isolates from the US (n=97), the MRSA rate was 30.9% and all isolates were lefamulin-susceptible (Table 1).

Figure 1. Lefamulin MIC distributions for methicillin-susceptible (MSSA) and methicillin-resistant *S. aureus* (MRSA) from children with cystic fibrosis

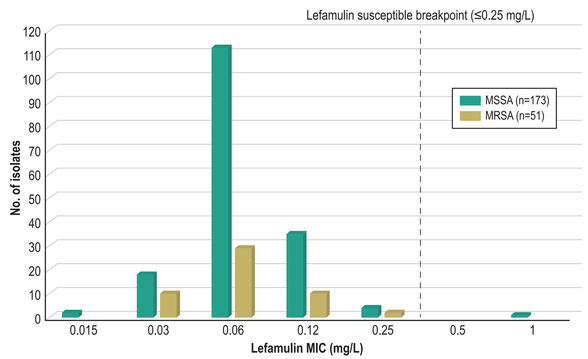

Figure 2. Lefamulin MIC distributions for resistant subsets of *S. aureus* from children with cystic fibrosis

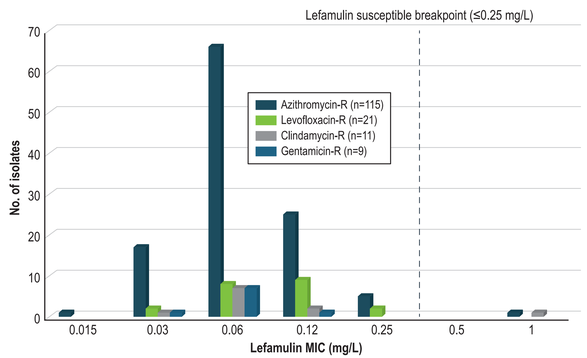

Table 1. Antimicrobial activity of lefamulin and comparator agents against *S. aureus* isolates from children with cystic fibrosis stratified by geographic region

Antimicrobial Agent	All *S. aureus* (224)		US (97)	EU (109)	LATAM (18)
	$MIC_{50/90}$ (mg/L)	% Susc.	% Susc.	% Susc.	% Susc.
Lefamulin	0.06/0.12	99.6	100.0	100.0	94.4
Azithromycin	8/>8	48.7	50.5	49.5	33.3
Ceftaroline	0.25/1	100.0	100.0	100.0	100.0
Clindamycin	0.06/0.06	95.1	94.8	100.0	66.7
Doxycycline	≤0.06/0.5	99.1	100.0	99.1	94.4
Levofloxacin	0.25/2	88.4	83.5	95.4	72.2
Linezolid	1/2	100.0	100.0	100.0	100.0
Oxacillin	0.5/>2	77.2	69.1	89.9	44.4
TMP-SMX	≤0.5/≤0.5	99.6	99.0	100.0	100.0
Vancomycin	0.5/1	100.0	100.0	100.0	100.0

Abbreviations: US, United States; EU, Europe; LATAM, Latin America; TMP-SMX, trimethoprim-sulfamethoxazole.

Table 2. Antimicrobial activity of lefamulin and comparator agents against *S. aureus* isolates from children with cystic fibrosis stratified by oxacillin susceptibility

Antimicrobial Agent	MSSA (173)		MRSA (51)	
	$MIC_{50/90}$ (mg/L)	% Susc.	$MIC_{50/90}$ (mg/L)	% Susc.
Lefamulin	0.06/0.12	99.4	0.06/0.12	100.0
Azithromycin	1/>8	56.1	8/>8	23.5
Ceftaroline	0.25/0.25	100.0	1/1	100.0
Clindamycin	0.06/0.06	98.8	0.06/>2	82.4
Doxycycline	≤0.06/0.25	99.4	≤0.06/0.5	98.0
Levofloxacin	0.25/0.5	95.4	0.25/2	64.7
Linezolid	1/2	100.0	1/2	100.0
TMP-SMX	≤0.5/≤0.5	100.0	≤0.5/≤0.5	98.0
Vancomycin	0.5/1	100.0	1/1	100.0

Abbreviations: MSSA, methicillin-susceptible *S. aureus*; MRSA, methicillin-resistant *S. aureus*; TMP-SMX, trimethoprim-sulfamethoxazole.

CONCLUSIONS

- Lefamulin demonstrated potent *in vitro* antibacterial activity against *S. aureus* from children with CF exacerbation, regardless of resistance phenotype.
- Further evaluation of lefamulin, which is available for oral and IV administration, as a treatment option for CF patients with pulmonary exacerbation due to *S. aureus* infection is warranted.

ACKNOWLEDGEMENTS

This study was supported by Nabriva Therapeutics (www.nabriva.com). JMI Laboratories received compensation fees for services related to preparing this poster.

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