FRIDAY - 345

In Vitro Activity of Lefamulin against Bacterial Pathogens Commonly Causing Pneumonia Collected from Patients in Asia (2015)

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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 inhibits bacterial protein synthesis and its antibacterial profile includes atypical organisms such as *Mycoplasma pneumoniae*, *Chlamydophila pneumoniae* and *Legionella pneumophila*. This study investigated the activity of lefamulin and comparators against contemporary typical respiratory pathogens collected from the Asia Pacific (APAC) region.

Methods: Unique patients' isolates (*n*=684) were collected during the 2015 SENTRY surveillance program at 13 sites in the APAC region (Australia, Korea, Malaysia, New Zealand, Singapore, Taiwan) from patients with respiratory tract infections (93.3%), bloodstream infections (4.1%), and other infections (2.6%). Lefamulin and comparators were tested by CLSI broth microdilution methods, and susceptibility was determined using CLSI (2017) breakpoints.

Results: Lefamulin displayed potent *in vitro* activity against *S. pneumoniae*, *M. catarrhalis* and *H. influenzae*. *S. pneumoniae* isolates were highly susceptible (S) to levofloxacin (98.7%) and amoxicillin/clavulanic acid (88.7%), but only 66.0% were S to macrolides, 57.0% to penicillin (at ≤0.06 mg/L) and 67.0% to tetracycline. Among *H. influenzae* isolates, susceptibility rates were generally higher (azithromycin, 100%; amoxicillin/clav, 92.2%; levofloxacin, 99.4%) except for ampicillin (64.9%) and trimethoprim-sulfamethoxazole (57.8%). All (100%) *M. catarrhalis* were susceptible to macrolides, ß-lactams, fluoroquinolones and tetracyclines. Lefamulin's activity was not affected by resistance to macrolides, ß-lactams, fluoroquinolones or tetracyclines.

Conclusion: Lefamulin demonstrated potent activity against bacteria commonly causing respiratory tract infections collected from patients in APAC, including resistant strains. These data together with the known activity against atypical respiratory pathogens supports further development of lefamulin for the treatment of CABP in APAC.

Table 1. $MIC_{50/90}$ [mg/L] of lefamulin and comparators

Organisms (no. of isolates)	Lefamulin	Amoxi/Clav	Azithro-mycin	Levo -floxacin
***S. pneumoniae* (309)**	0.06 / 0.12	≤0.03 / 4	0.06 / >4	1 / 1
Penicillin non-susc. (133) [a]	0.06 / 0.12	1 / >4	>4 / >4	1 / 1
Macrolide resistant (105)	0.06 / 0.12	1 / >4	>4 / >4	1 / 1
***S. aureus* (128)**	0.06 / 0.12	ND	0.5 / >4	0.25 / >4
MRSA (60)	0.06 / 0.12	ND	>4 / >4	>4 / >4
Macrolide- and levofloxacin-resistant MRSA (39)	≤0.03 / 0.12	ND	>4 / >4	>4 / >4
***H. influenzae* (154)**	0.5 / 1	1 / 4	1 / 1	≤0.015 / ≤0.015
***M. catarrhalis* (93)**	0.06 / 0.12	0.12 / 0.25	0.015 / 0.03	0.03 / 0.06

[a], Used oral penicillin breakpoints (S at ≤0.06 mg/L) according to CLSI (2017)

INTRODUCTION

CABP is a major cause of adult mortality in Asia with an estimate of one million adult deaths per year.[1] The aetiology of CABP in Asia is similar to that reported in the West in that *S. pneumoniae*, *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *H. influenzae* are significant aetiological agents.[1,2] Increasing resistance rates to commonly used antibiotics in many APAC countries complicate treatment, increase the severity of disease and often prolong hospital stays.[1]

Lefamulin is a novel representative of pleuromutilin class antibiotics. Pleuromutilins inhibit bacterial protein synthesis of Gram-positive and Gram-negative organisms. 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" (Figure 1).[3] Lefamulin's antibacterial profile includes activity against typical and atypical respiratory pathogens, including *C. pneumoniae* and *M. pneumoniae* (Table 2), against which lefamulin shows bactericidal activity.[4-6] Currently, lefamulin is in late stage development for the treatment of CABP.

This study investigated the *in vitro* activity of lefamulin against pathogens commonly causing pneumonia collected from patients in APAC region as part of the SENTRY surveillance program.

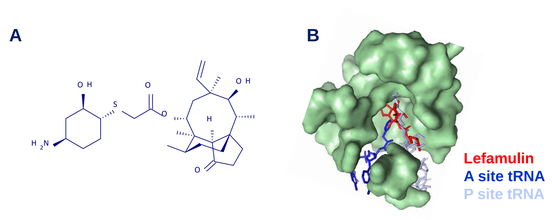

Figure 1. (A) Structure of lefamulin and (B) lefamulin in the PTC

Table 2. *In vitro* activity of lefamulin against *Mycoplasma pneumoniae* (Waites KB, *et al.*, 2017) [4]

M. pneumoniae, total	N	MIC_{50} [mg/L]	MIC_{90} [mg/L]	Range [mg/L]
Lefamulin	60	≤0.001	0.002	≤0.001 - 0.008
Azithromycin	60	16	>32	≤0.001 - >32
Moxifloxacin	50	0.125	0.25	0.063 - 0.25
Tetracycline	50	0.5	1	0.25 - 1

RESULTS

Table 3. *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. pneumoniae* (309)**							
Lefamulin	0.06	0.12	0.25	0.015 to 0.5	-	-	-
Amoxicillin/Clav.	≤0.03	4	>4	≤0.03 to >4	88.7	5.2	6.1
Azithromycin	0.06	>4	>4	≤0.03 to >4	66.0	0.3	33.7
Ceftaroline	≤0.008	0.12	0.5	≤0.008 to >1	99.4	-	-
Ceftriaxone	0.03	1	>2	≤0.015 to >2	91.9	6.5	1.6 [b]
Clindamycin	≤0.12	>1	>1	≤0.12 to >1	73.5	0.3	26.2
Cotrimoxazole	≤0.5	>4	>4	≤0.5 to >4	6.3	7.4	26.2
Erythromycin	0.03	>2	>2	≤0.015 to >2	66.0	0.0	34.0
Levofloxacin	1	1	4	0.25 to >4	98.7	0.3	1.0
Penicillin	≤0.06	2	8	≤0.06 to 8	57.0	24.9	18.1 [c]
Tetracycline	0.25	>4	>4	≤0.12 to >4	67.0	1.3	31.7
***S. aureus* (128)**							
Lefamulin	0.06	0.12	1 [d]	≤0.03 to >1	-	-	-
Azithromycin	0.5	>4	>4	0.12 to >4	60.2	2.3	37.5
Ceftaroline	0.25	2	2	≤0.06 to 4	78.1	21.1	0.8
Clindamycin	≤0.25	>2	>2	≤0.25 to >2	73.4	0.0	26.6
Doxycycline	≤0.06	8	8	≤0.06 to >8	82.8	16.4	0.8
Erythromycin	0.25	>8	>8	≤0.06 to >8	60.2	5.5	34.4
Levofloxacin	0.25	>4	>4	≤0.03 to >4	62.5	0.0	37.5
Linezolid	1	1	2	0.25 to 2	100.0	-	0.0
Oxacillin	0.5	>2	>2	≤0.25 to >2	53.1	-	46.9
Vancomycin	0.5	1	1	0.25 to 1	100.0	0.0	0.0
***H. influenzae* (154)**							
Lefamulin	0.5	1	2	≤0.12 to 4	-	-	-
Amoxicillin/Clav.	1	4	16	≤0.12 to 16	92.2	-	7.8
Ampicillin	0.5	>8	>8	0.12 to >8	64.9	1.9	33.1 [e]
Azithromycin	1	1	2	0.12 to 4	100.0	-	-
Ceftriaxone	≤0.015	0.06	0.25	≤0.015 to 0.25	100.0	-	-
Clarithromycin	8	8	16	0.5 to 16	94.8	5.2	0.0
Levofloxacin	≤0.015	≤0.015	0.5	≤0.015 to >2	99.4	-	-
Tetracycline	0.5	0.5	16	≤0.12 to >16	96.1	0.6	3.2
Cotrimoxazole	0.06	>4	>4	≤0.03 to >4	57.8	8.4	33.8
***M. catarrhalis* (93)**							
Lefamulin	0.06	0.12	0.25	≤0.008 to 0.25	-	-	-
Amoxicillin/Clav.	0.12	0.25	0.25	≤0.03 to 0.25	100.0	-	0.0
Azithromycin	0.015	0.03	0.06	0.008 to 0.06	100.0	-	-
Ceftriaxone	0.25	0.5	0.5	≤0.015 to 0.5	100.0	-	-
Erythromycin	0.12	0.12	0.5	≤0.015 to 0.5	100.0	-	-
Levofloxacin	0.03	0.06	1	≤0.015 to 1	100.0	-	-
Tetracycline	0.25	0.25	0.25	0.12 to 0.25	100.0	0.0	0.0

[a], Criteria as published by CLSI [2017] [8]; [b], Non-meningitis breakpoints applied for penicillin; [c], Oral breakpoints applied; [d], all except 2 isolates (98.4%) inhibited at ≤0.25mg/L; [e], ß-lactamase positive

RESULTS continued

- Lefamulin demonstrated potent antibacterial activity against this collection of respiratory clinical isolates collected from patients in APAC region in 2015 (Table 3).
- Lefamulin was highly active against *S. pneumoniae* with 100% of isolates being inhibited at a lefamulin concentration of 0.5 mg/L ($MIC_{50/90}$ of 0.06/0.12 mg/L). Lefamulin's potency was not affected by the presence of penicillin-or macrolide-resistance (Table 1).
- *S. pneumoniae* isolates were susceptible to ceftaroline and levofloxacin (>99%), ceftriaxone (91.9%), amoxicillin/clavulanic acid (88.7%) whereas suceptibility to penicillin and macrolide antibiotics was significantly reduced (57.0% and 66.0%, respectively).
- Lefamulin showed potent activity against *S. aureus* with 98.4% of all isolates being inhibited at ≤0.25 mg/L regardless of their resistance phenotype. Isolates included 46.9% MRSA (71.7% macrolide-resistant).
- Potent *in vitro* activity of lefamulin was also shown against *H. influenzae* and *M. catarrhalis,* with 99% of *H. influenzae* being inhibited at a lefamulin concentration of 2 mg/L and with 100% of *M. catarrhalis* being inhibited at 0.25 mg/L.
- Susceptibility rates of *H. influenzae* to comparators were generally high, with the exception of ampicillin (64.9%) and cotrimoxazole (57.8%).
- All *M. catarrhalis* isolates were fully susceptible to the tested comparators.

CONCLUSIONS

- **Lefamulin displayed potent antibacterial activity against this contemporary collection of typical respiratory pathogens from Asia.**
- **The activity of lefamulin was not negatively influenced by resistance to other antibiotic classes including macrolides, ß-lactams, tetracyclines or fluoroquinolones.**
- **This potent activity against typical respiratory pathogens, as well as atypicals, such as *Mycoplasma pneumoniae, Chlamydophila pneumoniae* and *Legionella pneumophila* [5-6] and the availability of IV and oral formulations, warrants further evaluation of lefamulin for the treatment of CABP.**

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