CEM-101, a Novel Ketolide; In Vitro Activity Against *Legionella pneumophila*

Topic 22 Poster # 903

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Abstract

Objective: CEM-101 is a new fluoroketolide that has potent activity against respiratory tract pathogens. The activity against a variety of *Legionella pneumophila* serogroup was investigated.

Methods: The *in vitro* activity of **CEM-101** was compared with that of telithromycin, azithromycin, erythromycin, levofloxacin and doxycycline against a total of 300 *Legionella pneumophila* by a standard agar dilution procedure using buffered yeast extract agar. The species tested included *L. pneumophila* serogroup 1 (125 isolates), serogroup 2 (28), 3 (25), 4 (36), 5 (25), 6 (50) and serogroup 7,8,9,12 (11).

Results: CEM-101 (MIC90 0.016 mg/L) was as active as levofloxacin (MIC90 0.016 mg/L) against *L. pneumophila* and was more active than telithromycin (MIC90 0.06 mg/L), azithromycin (MIC90 0.25 mg/L), erythromycin (MIC90 1 mg/L) and doxycycline (MIC90 1 mg/L). Against the most frequent *L. pneumophila* such as serogroup 1, the MIC90 of **CEM-101** (0.03 mg/L) was superior to telithromycin (0.06 mg/L), azithromycin (0.5 mg/L), erythromycin (1 mg/L) and doxycycline (1 mg/L). Against *L. pneumophila* serogroup 1, the MIC90 of **CEM-10**1 (0.03 mg/L) was similar to levofloxacin (0.016 mg/L). **CEM-101** was less active against *L. pneumophila* serogroup 1, 2, 3, 4, 5, and 6 strains (MIC90 0.016 mg/L) than *L. pneumophila* serogroup 7, 8, 9 and 12 (MIC90 0.008 mg/L).

Conclusions: These data confirm the interesting activity of this new fluoroketolide **CEM-101** against *Legionella pneumophila*..
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Introduction

CEM-101 is a novel fluoroketolide antibacterial agent related to 14-membered ring macrolides. **CEM-101** appears to exhibit superior ability to bind to the ribosomes dimethylated at A2058 by the action of *erm* methyltransferase.

In susceptibility studies, **CEM-101** is appreciably more potent than most macrolides or azalides against many Gram-positive organisms, including resistant *Streptococcus pneumoniae, Streptococcus pyogenes* and *Staphylococcus* spp. It has potent activity against various atypical respiratory pathogens like *Legionella pneumophila*, *Mycoplasma* spp. and *Chlamydia* spp.

Objective

We determined the minimum inhibitory concentration (MIC) of **CEM-101,** telithromycin, azithromycin, erythromycin, doxycycline and levofloxacin against a variety of *Legionella pneumophila* isolated from nosocomial or acquired respiratory tract infections.

Materials and Methods

Strains

A variety of *Legionella pneumophila* were collected from mostly respiratory tract sources from 1988 to present.
Multiple cultures from the same patient or source were excluded unless a change in organism or antibiogram was noted.
Organisms were identified by standard methods such as described by Murray et al. (1).

Microorganisms	Maximum Number of tested strains
1. *L. pneumophila* All serogroup	300
2. *L. pneumophila* serogroup 1	125
3. *L. pneumophila* serogroup 2	28
4. *L. pneumophila* serogroup 3	25
5. *L. pneumophila* serogroup 4	36
6. *L. pneumophila* serogroup 5	25
7. *L. pneumophila* serogroup 6	50
8. *L. pneumophila* serogroup 7,8,9, 12	11

Determination of MICs

MICs were determined using the CLSI agar dilution method (2, 3), with replicate plating of the organisms onto a series of agar plates of increasing concentrations from 0.004 mg/L to 64 mg/L.
Buffered Yeast extract (BYE) was used as the medium against *Legionella* strains.
Staphylococcus aureus ATCC25923, *Pseudomonas aeruginosa* ATCC27853 and *Legionella pneumophila* ATCC33152 have been included as controls.

Results

TABLE 1. Susceptibility of *Legionella pneumophila*

Organism (no. tested)	Antibiotic	MIC (mg/L) Range	50%	90%
L.pneumophila All serogroup (300)	**CEM-101**	≤0.004-0.06	0.008	0.016
	Telithromycin	0.016-0.12	0.03	0.06
	Azithromycin	0.008-1	0.06	0.25
	Erythromycin	0.008-2	0.25	1
	Levofloxacin	≤0.004-0.03	0.008	0.016
	Doxycycline	0.5-1	1	1
L.pneumophila serogroup 1 (125)	**CEM-101**	≤0.004-0.06	0.016	0.03
	Telithromycin	0.016-0.12	0.03	0.06
	Azithromycin	0.016-1	0.12	0.5
	Erythromycin	0.06-2	25	1
	Levofloxacin	≤0.004-0.03	0.016	0..016
	Doxycycline	0.5-1	1	1
L.pneumophila serogroup 2 (28)	**CEM-101**	≤0.004-0.03	0.008	0.016
	Telithromycin	0.016-0.06	0.016	0.03
	Azithromycin	0.008-0.12	0.06	0.12
	Erythromycin	0.008-0.5	0.25	0..25
	Levofloxacin	≤0.004-0.016	0.008	0..008
	Doxycycline	0.5-1	1	1
L.pneumophila serogroup 3 (25)	**CEM-101**	≤0.004-0.016	0.008	0.016
	Telithromycin	0.016-0.06	0.03	0..03
	Azithromycin	0.016-0.25	0.12	0.25
	Erythromycin	0.12-0.5	0.25	0.5
	Levofloxacin	≤0.004-0.016	0.008	0..008
	Doxycycline	0.5-1	1	1

Results continued

TABLE 2. Susceptibility of *Legionella pneumophila* serogroup 4, 5, 6 and others serogroup (7, 8, 9 and 12)

Organism (no. tested)	Antibiotic	MIC (mg/L) Range	50%	90%
L.pneumophila serogroup 4 (36)	**CEM-101**	≤0.004-0.03	0.008	0.016
	Telithromycin	0.016-0.06	0.03	0..03
	Azithromycin	0.016-0.25	0.12	0..12
	Erythromycin	0.06-0.5	0.5	0..5
	Levofloxacin	≤0.004-0.016	0.016	0..016
	Doxycycline	0.5-1	1	1
L.pneumophila serogroup 5 (25)	**CEM-101**	≤0.004-0.03	0.008	0.016
	Telithromycin	0.03-0.06	0.06	0..06
	Azithromycin	0.008-0.5	0.03	0.5
	Erythromycin	0.06-1	0.25	0.5
	Levofloxacin	≤0.004-0.016	0.008	0.016
	Doxycycline	0.5-1	1	1
L.pneumophila serogroup 6 (50)	**CEM-101**	≤0.004-0.03	0.008	0.016
	Telithromycin	0.016-0.06	0.016	0.03
	Azithromycin	0.03-0.25	0.06	0.12
	Erythromycin	0.008-0.25	0.12	0.25
	Levofloxacin	0.008-0.016	0.008	0.016
	Doxycycline	0.5-1	1	1
L.pneumophila serogroup 7,8,9, 12 (11)	**CEM-101**	≤0.004-0.008	0.008	0..008
	Telithromycin	0.016-0.06	0.03	0.06
	Azithromycin	0.06	0..06	0..06
	Erythromycin	0.12-0.5	0.25	0.5
	Levofloxacin	0.008-0.016	0.016	0..016
	Doxycycline	0.5-1	1	1

Discussion

- **CEM-101** (MIC_{90} 0.016 mg/L) was significantly more potent than the most commonly used drugs for the treatment of Legionellosis, such as erythromycin and azithromycin.
- Among the antimicrobial agents tested, levofloxacin (MIC_{90} 0.016 mg/L) was the only antimicrobial agent that was comparable to **CEM-101** against *Legionella pneumophila*.
- Against *L. pneumophila*, **CEM-101** (MIC_{90} 0.016 mg/L) was significantly more active than erythromycin (MIC_{90} 1 mg/L) , azithromycin (MIC_{90} 0.25 mg/L) and doxycycline (MIC_{90} 1 mg/L) and slightly more active than telithromycin (MIC_{90} 0.06 mg/L).
- *L. pneumophila* serogroup 1 was more resistant to **CEM-101** (MIC_{90} 0.3 mg/L) than other *L. pneumophila* serogroup.
- The activity of **CEM-101** against *L. pneumophila* serogroup 1 was particularly interesting, in that this serogroup is the most resistant strain to erythromycin (MIC_{90} 1 mg/L) and the most common strain isolated from nosocomial or acquired respiratory tract infections.
- Against *L. pneumophila* serogroup 5, azithromycin and erythromycin were less active (MIC_{90} 0.5 mg/L) than other ketolide tested: CEM-101 (MIC_{90} 0.016 mg/L) and telithromycin (MIC_{90} 0.06 mg/L).
- *L. pneumophila* serogroup 7,8,9 and 12 were the most *L. pneumophila* serogroup susceptible to **CEM-101** (MIC_{90} 0.008 mg/L) .

Conclusion

- **CEM-101** should be a promising agent for the treatment of lower respiratory tract infections caused by *Legionella pneumophila*.
- Clinical studies should undertaken to evaluate the *in vivo* effectiveness of this new antimicrobial agent.

References

1. Murray et al., Manual of Clinical Microbiology, 9rd ed., 2007, A.S.M. Chap. 53; 835-849.
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3. Method for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard 17th edition, M7-A7, Clinical and Laboratory Standards Institute (CLSI), Wayne, PA, 2006)