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In Vitro Activity of CEM-101 Against *Legionella spp.*

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Revised Abstract

Background: CEM-101 is a new fluoroketolide that has potent activity against respiratory tract pathogens. Its activity against a variety of *Legionella* species 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 410 *Legionella* spp. by a standard agar dilution procedure using buffered yeast extract agar. The species tested included *L. pneumophila* serogroups 1 to 12 (300 isolates), *L. dumoffii* (30), *L. micdadei* (30) and *L. longbeacheae* (25).
Results: Against the *L. pneumophila* strains tested, CEM-101 (MIC_{90} 0.016 mg/L) was more active than telithromycin (MIC_{90} 0.06 mg/L), azithromycin (MIC_{90} 0.25 mg/L), erythromycin (MIC_{90} 1 mg/L) and doxycycline (MIC_{90} 1 mg/L). CEM-101 was as active as levofloxacin (MIC_{90} 0.016 mg/L) against *L. pneumophila*. CEM-101 was less active against *L. pneumophila* serogroup 1, 2, 3, 4, 5, and 6 strains (MIC_{90} 0.016 mg/L) than *L. pneumophila* serogroup 7, 8, 9 and 12 strains (MIC_{90} 0.008 mg/L). Against *L. micdadei* and *L. dumoffii* , erythromycin (MIC_{90} 1 mg/L), doxycycline (MIC_{90} 1 mg/L) and azithromycin (MIC_{90} 0.25 mg/L) were less active than CEM-101 (MIC_{90} 0.12 mg/L) and telithromycin (MIC_{90} 0.12 mg/L). Against *L. longbeacheae*, CEM-101 (MIC_{90} 0.06 mg/L) was more active than levofloxacin (MIC_{90} 0.12 mg/L), telithromycin (MIC_{90} 0.12 mg/L), azithromycin (MIC_{90} 0.12 mg/L), erythromycin (MIC_{90} 0.5 mg/L) and doxycycline (MIC_{90} 1 mg/L).
Conclusions: These data confirm the interesting activity of this new fluoroketolide, CEM-101, against *Legionella spp.*

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 2058 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* isolated from nosocomial or acquired respiratory tract infections or from environmental sources.

Materials and Methods

Strains

- A variety of *Legionella* were collected from respiratory tract or environmental 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*	300*
2. *L. micdadei*	30
3. *L. dumoffii*	30
4. *L. longbeacheae*	25
5. *L.* others (*bozemanae, feeleii gormanii, oakridgensis, sainthelensi, anisa, wadsworthii*)	25

*10 different serogroups

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	0.25	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

Results continued

TABLE 3. Susceptibility of *Legionella* other than *pneumophila*

Organism (no. tested)	Antibiotic	MIC (mg/L) Range	50%	90%
L. dumoffii (30)	**CEM-101**	≤0.004-0.12	0.06	0.12
	Telithromycin	0.06-0.12	0.12	0.12
	Azithromycin	0.12-0.25	0.12	0.25
	Erythromycin	0.25-0.5	0.25	0.5
	Levofloxacin	0.008-0.016	0.016	0.016
	Doxycycline	0.5-1	0.5	0.5
L. micdadei (30)	**CEM-101**	≤0.004-0.12	0.016	0.12
	Telithromycin	0.016-0.06	0.06	0.06
	Azithromycin	0.016-0.25	0.25	0.25
	Erythromycin	0.5-1.0	0.5	1
	Levofloxacin	0.008-0.016	0.016	0.016
	Doxycycline	0.06-1	0.12	1
L. longbeacheae (25)	**CEM-101**	≤0.004-0.12	0.008	0.06
	Telithromycin	0.06-0.12	0.12	0.12
	Azithromycin	0.016-0.25	0.12	0.12
	Erythromycin	0.12-0.5	0.25	0.5
	Levofloxacin	0.008-0.12	0.016	0.12
	Doxycycline	0.06-1	0.25	1
L. other than *pneumophila dumoffii, micdadei* and *longbeacheae* (25)*	**CEM-101**	≤0.004-0.03	≤0.004	0.016
	Telithromycin	0.06-0.12	0.12	0.12
	Azithromycin	0.03-0.25	0.12	0.25
	Erythromycin	0.25-1	0.5	1
	Levofloxacin	0.008-0.016	0.016	0.016
	Doxycycline	0.03-1	1	1

* *L.* other than *pneumophila* included: *L.* others (*bozemanae* (5 strains), *feeleii* (5 strains), *gormanii* (5 strains), *oakridgensis* (3 strains) , *sainthelensi* (3 strains), *anisa* (2 strains), *wadsworthii* (2 strains).

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* species.
- 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* serogroups.
- 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.
- The activity of CEM-101 against *Legionella* other than *pneumophilia* was similar to its activity against *pneumophilia*.
- Among those species tested, *L. longbeacheae* was the most susceptible species to **CEM-101** (MIC_{90} 0.06 mg/L); erythromycin (MIC_{90} 0.5 mg/L) and doxycycline (MIC_{90} 1 mg/L) were less active than **CEM-101**.
- Against *L. longbeacheae*, **CEM-101** (MIC_{90} 0.06 mg/L) was slightly more active than levofloxacin, telithromycin and azithromycin (all with MIC_{90} 0.12 mg/L).
- **CEM-101** (MIC_{90} 0.12 mg/L) was markedly more active against *L. dumoffii* and *L. micdadei* than erythromycin and doxycycline (MIC_{90} 0.5 - 1 mg/L) . The activity of **CEM-101** was similar to the activity of telithromycin against these species.

Conclusion

- **CEM-101** should be a promising agent for the treatment of lower respiratory tract infections caused by *Legionella* spp.
- 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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