

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. longbeachae* (25).

Results: Against the *L. pneumophila* strains tested, CEM-101 (MIC₉₀ 0.016 mg/L) 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). CEM-101 was as active as levofloxacin (MIC₉₀ 0.016 mg/L) against *L. pneumophila*. 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 strains (MIC₉₀ 0.008 mg/L). Against *L. micdadei* and *L. dumoffii*, erythromycin (MIC₉₀ 1 mg/L), doxycycline (MIC₉₀ 1 mg/L) and azithromycin (MIC₉₀ 0.25 mg/L) were less active than CEM-101 (MIC₉₀ 0.12 mg/L) and telithromycin (MIC₉₀ 0.12 mg/L). Against *L. longbeachae*, CEM-101 (MIC₉₀ 0.06 mg/L) was more active than levofloxacin (MIC₉₀ 0.12 mg/L), telithromycin (MIC₉₀ 0.12 mg/L), azithromycin (MIC₉₀ 0.12 mg/L), erythromycin (MIC₉₀ 0.5 mg/L) and doxycycline (MIC₉₀ 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. <i>L. pneumophila</i> | 300* |
| 2. <i>L. micdadei</i> | 30 |
| 3. <i>L. dumoffii</i> | 30 |
| 4. <i>L. longbeachae</i> | 25 |
| 5. <i>L. others (bozemanæ, feeleii gormanii, oakridgensis, sainthelensi, anisa, wadsworthii)</i> | 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% |
| <i>L. pneumophila</i> 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 |
| <i>L. pneumophila</i> 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 |
| <i>L. pneumophila</i> 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 |
| <i>L. pneumophila</i> 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% |
| <i>L. pneumophila</i> 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 |
| <i>L. pneumophila</i> 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 |
| <i>L. pneumophila</i> 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 |
| <i>L. pneumophila</i> 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% |
| <i>L. dumoffii</i> (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 |
| <i>L. micdadei</i> (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 |
| <i>L. longbeachae</i> (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 |
| <i>L. other than pneumophila dumoffii, micdadei and longbeachae</i> (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 (bozemanæ (5 strains), feeleii (5 strains), gormanii (5 strains), oakridgensis (3 strains), sainthelensi (3 strains), anisa (2 strains), wadsworthii (2 strains).*

Discussion

- CEM-101 (MIC₉₀ 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 (MIC₉₀ 0.016 mg/L) was the only antimicrobial agent that was comparable to CEM-101 against *Legionella* species.
- Against *L. pneumophila*, CEM-101 (MIC₉₀ 0.016 mg/L) was significantly more active than erythromycin (MIC₉₀ 1 mg/L), azithromycin (MIC₉₀ 0.25 mg/L) and doxycycline (MIC₉₀ 1 mg/L) and slightly more active than telithromycin (MIC₉₀ 0.06 mg/L).
- L. pneumophila* serogroup 1 was more resistant to CEM-101 (MIC₉₀ 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 (MIC₉₀ 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 *pneumophila* was similar to its activity against *pneumophila*.
- Among those species tested, *L. longbeachae* was the most susceptible species to CEM-101 (MIC₉₀ 0.06 mg/L); erythromycin (MIC₉₀ 0.5 mg/L) and doxycycline (MIC₉₀ 1 mg/L) were less active than CEM-101.
- Against *L. longbeachae*, CEM-101 (MIC₉₀ 0.06 mg/L) was slightly more active than levofloxacin, telithromycin and azithromycin (all with MIC₉₀ 0.12 mg/L).
- CEM-101 (MIC₉₀ 0.12 mg/L) was markedly more active against *L. dumoffii* and *L. micdadei* than erythromycin and doxycycline (MIC₉₀ 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

- Murray et al., Manual of Clinical Microbiology, 9rd ed., 2007, A.S.M. Chap. 53; 835-849.
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