Poster # 904

CEM-101, a Novel Ketolide: In Vitro Activity Against Resistant Strains of *Streptococcus pneumoniae* and *Haemophilus influenzae*

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Abstract

Objective: CEM-101 is a promising fluoroketolide that has potent activity against respiratory tract pathogens resistant to other macrolide agents. Its activity against a variety of resistant strains of *Streptococcus pneumoniae* and *Haemophilus influenzae* 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 199 resistant *S. pneumoniae* and 191 resistant *H. influenzae* by agar dilution procedures (CLSI, M7-A7, M100-S18). The tested strains included *S. pneumoniae* erythromycin-resistant (*erm* B genotype; 107 isolates and *mef*E genotype; 54) and ciprofloxacin-resistant (gyrA and *par*C genotype; 38) and also *H. influenzae* ery-resistant (*erm* A,B,C genotype; 138) and cipro-resistant (gyrA and *par*C genotype; 53) .
Results: Against *S. pneumoniae* ery-resistant strains (*ermB* genotype), the activity of **CEM-101** (MIC90 1mg/L) and levofloxacin (MIC90 2mg/L) was superior to the macrolides tested: telithromycin (MIC90 4mg/L), azithromycin (MIC90 ≥64 mg/L), erythromycin (MIC90 ≥64 mg/L)) and doxycycline (MIC90 32 mg/L). Against *S. pneumoniae* ery-resistant (*mef*E genotype) group, **CEM-101** (MIC90 0.25 mg/L) was the most active agent followed by levofloxacin (MIC90 2mg/L), telithromycin (MIC90 8 mg/L), doxycycline (MIC90 16 mg/L), azithromycin (MIC90 ≥64 mg/L) and erythromycin (MIC90 ≥64 mg/L). Against *S. pneumoniae* cipro-resistant (gyrA and *par*C genotype) group, **CEM-101** (MIC90 0.25 mg/L) was also the most active agent tested followed by telithromycin (MIC90 1 mg/L), levofloxacin (MIC90 2mg/L), doxycycline (MIC90 16 mg/L), azithromycin (MIC90 ≥64 mg/L) and erythromycin (MIC90 ≥64 mg/L). Against *H. influenzae* ery-resistant (*erm*A,B,C genotype) strains, **CEM-101** (MIC90 4 mg/L) was the most active macrolide tested followed by telithromycin (MIC90 16 mg/L), azithromycin (MIC90 16 mg/L) and erythromycin (MIC90 ≥64 mg/L). Against *H. influenzae* cipro-resistant (gyrA and *par*C genotype) group, **CEM-101** (MIC90 2 mg/L) was slightly more active than telithromycin (MIC90 4 mg/L) and levofloxacin (MIC90 4 mg/L).
Conclusions: These data confirm the interesting activity of the new fluoroketolide **CEM-101** against resistant *Streptococcus pneumoniae* and *Haemophilus influenzae*. .

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, levofloxacin and doxycycline against a variety of *Streptococcus pneumoniae* and *Haemophilus influenzae* strains isolated from patient sources.

Materials and Methods

Strains

- A variety of recent strains (1995-2008) of *Streptococcus pneumoniae* and *Haemophilus influenzae* were isolated, mostly from upper or lower respiratory tract or blood culture.
- 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	Number of tested strains
Streptococcus penumoniae	199
-Erythromycin-resistant (*mef* E genotype)	107
-Erythromycin-resistant (*erm* B genotype)	54
-Ciprofloxacin-resistant (gyrA and *par*C genotype)	38
Haemophilus influenzae	191
-Erythromycin-resistant (*erm*A, B, C genotype)	138
-Ciprofloxacin-resistant (gyrA and *par*C genotype)	53

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.
- Mueller-Hinton agar was used as the medium against *S. aureus* strains.
- *Staphylococcus aureus* ATCC25923 and *Escherichia coli* ATCC25922 were included as controls.

Determinations of genotype *mec A, ermA, B, C, mefE* and gyrA and *par*C

- Genomic DNA was isolated as described by Smith *et al* (4)
- Multiplex PCR was performed with primers specific for *mec A, ermA, ermB, ermC* and *mefE* as described by Sutcliffe *et al* (5)
- Multiplex PCR was performed with primers specific for *gyrA* and *par*C as described by Gonzalez *et al* (6)

Results

TABLE 1. Susceptibility of *Streptococcus pneumoniae*

Organism (no. tested)	Antibiotic	MIC (mg/L) Range	50%	90%
S. pneumoniae Erythromycin-R *mef* E (107)	**CEM-101**	0.016-2	0.25	1
	Telithromycin	0.06-32	1	4
	Azithromycin	4-≥64	≥64	≥64
	Erythromycin	0.06-≥64	≥64	≥64
	Levofloxacin	0.25-2	1	2
	Doxycycline	0.06-32	16	32
S. pneumoniae Erythromycin-R *erm* B (54)	**CEM-101**	0.008-2	0.06	0.25
	Telithromycin	0.12-8	0.25	8
	Azithromycin	0.008-≥64	4	≥64
	Erythromycin	0.06-≥64	16	≥64
	Levofloxacin	0.5-2	1	2
	Doxycycline	0.12-32	4	16
S. pneumoniae Ciprofloxacin-R *gyrA, parC* (38)	**CEM-101**	0.016-0.25	0.03	0.25
	Telithromycin	0.06-2	0.12	1
	Azithromycin	0.12-≥64	0.25	≥64
	Erythromycin	0.12-≥64	0.25	≥64
	Levofloxacin	1-4	2	2
	Doxycycline	0.06-32	0.5	16

Results continued

TABLE 2. Susceptibility of *Haemophilus influenzae*

Organism (no. tested)	Antibiotic	MIC (mg/L) Range	50%	90%
H influenzae Erythromycin-R erm A,B,C (138)	**CEM-101**	0.12-8	4	4
	Telithromycin	0.25-≥64	8	16
	Azithromycin	0.12-≥64	8	16
	Erythromycin	0.25-≥64	32	≥64
	Levofloxacin	0.008-0.016	0.016	0.016
	Doxycycline	0.12-2	0.5	0.5
H. influenzae Ciprofloxacin-R *gyrA, parC* (53)	**CEM-101**	0.12-4	1	2
	Telithromycin	0.25-16	2	4
	Azithromycin	0.25-8	1	2
	Erythromycin	0.25-16	1	2
	Levofloxacin	1-8	2	4
	Doxycycline	0.03-0.5	0.25	0.5

Discussion

- **CEM-101** showed significant activity (MIC_{90} ≤1 mg/L) against categorized *Streptococcus pneumoniae* strains, including strains that were resistant to macrolides (*erm* B or *mef* E genotype) or quinolones.
- Against erythromycin-resistant (*erm* B genotype) *S. pneumoniae,* **CEM-101** was significantly superior to the antibiotics tested: telithromycin, azithromycin and erythromycin, doxycycline and levofloxacin.
- When *S. pneumoniae* ciprofloxacin-resistant (gyrA and *par*C genotype) strains were treated with **CEM-101**, this new macrolide exerted greater activity (MIC_{90} 0.25 mg/L) and was superior to doxycycline. This observation was not seen with the other tested macrolides.
- The activity (MIC_{90} 4 mg/L) of **CEM-101** was clearly superior to all macrolides tested (MIC_{90} ≥16 mg/L) against erythromycin-resistant *H. I nfluenzae* (*ermA, B, C* genotype).

Conclusion

- **CEM-101** shows a broad spectrum of activity against the most commonly isolated resistant strains of *S. pneumoniae* or *H. influenzae* isolated from respiratory tract infections.
- With favorable pharmacokinetics in humans, **CEM-101** should be a valuable oral compound for the treatment of upper or lower respiratory tract infections caused by *S. pneumoniae* or *H. influenzae* that are resistant to standard oral macrolides or quinolones.
- Clinical studies should undertaken to evaluate the *in vivo* effectiveness of this new antimicrobial agent.

References

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