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Comparative activities of the novel ketolide CEM-101 and telithromycin (TEL) towards *Streptococcus pneumoniae* (SP) resistant to macrolides (ML) from patients with confirmed community-acquired pneumonia (CAP).

A. Lismond, F. Van Bambeke, P.M. Tulkens - Unité de Pharmacologie cellulaire et moléculaire, Université catholique de Louvain, Brussels, Belgium

Mailing address:
P. M. Tulkens
UCL 73.70 av. Mounier 73
1200 Brussels - Belgium
tulkens@facm.ucl.ac.be

ABSTRACT (edited)

Background and aims: CEM-101 is a new fluoroketolide in development with activity against macrolide (ML)-resistant isolates. A dose of 400 mg qD yields an AUC_{24h} similar to that of telithromycin (TEL) 800 mg qD and shows similar protein binding properties in human serum (about 15 % free drug). Belgium is a country with high resistance of SP to ML (> 35 % for clarithromycin). Our aim was to compare the activity of CEM-101 to that of TEL against ML-resistant strains of SP obtained from patients with confirmed CAP. .

Methods: 29 first ML-R isolates (based on clarithromycin MICs determination; 19 MLS_B, 10 M-phenotype based on erythromycin and clindamycin resistance dissociation) were selected (for which 6 were TEL-I and 7 TEL-R based on EUCAST breakpoints [S ≤ 0.25 - R > 0.5]). MICs were determined by geometric microdilution in CAMH broth + 2.5% lysed horse blood according to CLSI, using SP ATCC-49619 as a control.

Results:
ATCC-49619 MICs were ≤0.008 mg/L for TEL and CEM-101. Data for ML-resistant isolates are shown in the Table.

Phenotype*	No.	TEL			CEM-101		
		range	geom. mean	MIC_{90}	range	geom. mean	MIC_{90}
TEL-S	16	0.008-0.25	0.021	0.25	0.008-0.063	0.022	0.063
TEL-I	6	0.5-0.5	0.5	0.5	0.063-0.5	0.223	0.5
TEL-R	7	1-3	1.426	3.0	0.5-1.0	0.906	1.0

* MLS_B for 7/16 of TEL-S, 5/6 of TEL-I, and 7/7 of TEL-R isolates
(S / I / R are defined based on EUCAST breakpoints (S ≤ 0.25 – R > 0.5)

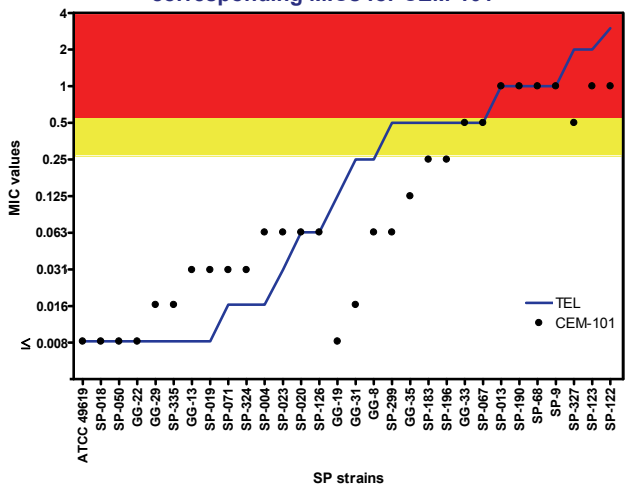
Conclusions: In this Belgian collection of *S. pneumoniae* from confirmed CAP resistant to macrolides, CEM-101 shows globally lower MICs compared to TEL, especially with respect to TEL-I and TEL-R isolates. CEM-101, therefore, has the potential to stand as an alternative to telithromcyin in areas with high ML resistance and emerging resistance to TEL.

Background and Aim

- CEM-101 is a new fluoroketolide in development with activity against macrolide (ML)-resistant isolates, yielding, at 400 mg qD, an AUC_{24h} similar to that of telithromycin at 800 mg qD. CEM-101 and TEL show similar protein binding in human serum (about 15 % free drug). Previous studies have shown that CEM-101, with MIC values ranging from 0.004 up to 1 µg/ml, can be up to four-fold more active than TEL against *S. pneumoniae* and that only ErmB strongly affects its activity (1).
- In Belgium, ~ 35% of *S. pneumoniae* isolates are resistant to macrolides and already 7.5% must be considered as having a "decreased susceptibility" to TEL telithromycin if using EUCAST breakpoints (2).
- Our aim was to compare the activity of CEM-101 to that of TEL against *S. pneumoniae* clinical strains selected for
  - decreased susceptibility to telithromycin (13 TEL-NS), and
  - distinct patterns of resistance to macrolides (7 MLS_B- and 9 M-phenotype) among TEL-S isolates.

Results

Strains ordered by increasing MIC for telithromycin with corresponding MICs for CEM-101



EUCAST breakpoint for TEL: S ≤ 0.25 (white) – I (yellow) – R>0.5 (red).

Range of CEM-101 MIC values and macrolides resistance phenotype according to telithromycin MICs.

	nbr of strains	MIC TEL (µg/ml)	range MIC CEM-101 (µg/ml)	Macrolides resistance phenotype	
				MLS_B	M
TEL-R	1	4	1	1	0
	3	2	0.5-1	3	0
	3	1	1	3	0
TEL-I	6	0.5	0.06-0.5	5	1
TEL-S	2	0.25	0.016-0.06	0	2
	1	0.125	≤0.008	0	1
	2	0.06	0.06	0	2
	1	0.03	0.06	1	0
	3	0.016	0.03-0.06	1	2
	7	≤0.008	≤0.008-0.03	5	2

MLS_B-phenotype (methylase Erm): resistance to macrolides, lincosamides and streptogramins B.

M-phenotype (efflux [Mef pump]): resistance to 14- and 15-membered-ring macrolides.

Methods

Bacteria: All of TEL-R (7) and TEL-I (5) isolates found in our collection of *S. pneumoniae* plus 16 TEl-S isolates with distinct macrolide resistance phenotypes (MLS_B or M) were also used for testing.

Susceptibility testing: CEM-101 was diluted in 0.1N HCl. MICs were determined by geometric microdilution in CAMH broth + 2.5% lysed horse blood following CLSI recommendations. *S. pneumoniae* ATCC 49619 was used as a quality control. Susceptibility was assessed according to EUCAST breakpoints. Clarithromycin and clindamycin were used to differentiate between MLS_B and M-phenotype. Active efflux of macrolides (M-phenotype) was evidenced by comparison with the MICs of CLR and CLI (only affected by ribosomal mutations or methylation).

Results

- Population analysis (graph): At MICs values of up to 0.06 µg/ml, TEL was more effective than CEM-101, while the inverse situation was seen at higher TEL MICs, whith all isolates showing lower or similar MIC values for CEM-101.
- Analysis by isolates: Isolates with MICs of 1 mg/L were observed only for TEL-R isolates (all with MLS_B-phenotype). Only one TEL-I isolate displayed an M-phenotype and its MIC for CEM-101 was 0.06 mg/L.
- No correlation was found between the macrolide resistance phenotype in the TEL-S isolates and the MIC of CEM-101.

Conclusions

- In this Belgian collection of *S. pneumoniae* resistant to macrolides, CEM-101 showed globally lower MICs compared to telithromycin, especially with respect to TEL-I and TEL-R isolates.
- CEM-101 has the potential to stand as an alternative to telithromycin in areas with high macrolide resistance and emerging resistance to telithromycin.

References

1. McGhee *et al.* Comparative activity of CEM-101 against macrolide-susceptible and –resistant pneumococci. 48th ICAAC & 46th IDSA, 25-28 Oct. 2008; F1-3974
2. Lismond *et al.* Epidemiological survey of susceptibility to β-lactams (AMX, CFX, CRO), macrolides (CLR, TEL), and fluoroquinolones (LVX, MXF) in a Belgian collection of CAP isolates of *Streptococcus pneumoniae* (SP). 18th ECCMID 19-22 April 2008; P-1747.

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