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Activity of Solithromycin (SOL) against *S. pneumoniae* (SP) clinical strains with non-susceptibility (NS) or resistance (R) [EUCAST interpretative criteria] to penicillin G (PEN), amoxicillin (AMX), ceftriaxone (CRO), moxifloxacin (MXF), levofloxacin (LVX) and ceftaroline (CPT)

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Abstract (edited)

Background.

SOL (also known as CEM-101) is a fluoroketolide active against macrolide-resistant SP and presently in phase 3 trial in community-acquired bacterial pneumonia (CABP). Our aim was to assess its vitro activity against RTI clinical SP isolates for which beta-lactams and fluoroquinolones can no longer be used.

Methods

Two large collections of non-duplicate RTI SP isolates from Belgium and Germany were screened with based on potential patient's risk for harboring beta-lactam- and fluoroquinolone-resistant strains. MICs for 426 isolates were measured by broth microdilution. Focusing on NS and R isolates, cross-resistance wit SOL was assessed by linear fit, bivariate normal ellipse analysis (0.90 overlap), and quantile density contour coincidence (QDCI; 0.1 to 0.9) using JMP software (version 10.0.2).

Results

The Table shown in the Results section of the poster shows (a) the MICs (min., geomean, 90 % and max.) of SOL, PEN, AMX, CRO, MXF, LVX and CPT for all isolates and (b) the pertinent results for strains NS or R to these antibiotics (EUCAST breakpoints) and the correlation parameters with the MICs of SOL for the corresponding isolates. 90 % ellipses were very wide (> 6 dilutions for minor axis [conjugate diameter]) and QDCI did not show evidence for high level MICs for SOL in strains with MICs > EUCAST NS or R breakpoints for other antibiotics.

Conclusions

SOL maintains low MICs for clinical SP isolates with NS and R phenotype to currently used or recently approved antibiotics for treatment of CABP with no statistically-significant correlation (except for MXF and, to some extent, for PEN, but note the low alpha parameter). SOL may, therefore, stand as a potentially useful alternative in environments where these antibiotics can no longer be recommended.

References

1. Van Bambeke *et al.* Multidrug-resistant Streptococcus pneumoniae infections: current and future therapeutic options. Drugs. 2007;67:2355-82
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3. Llano-Sotelo *et al.* Binding and action of CEM-101, a new fluoroketolide antibiotic that inhibits protein synthesis. Antimicrob Agents Chemother. 2010;54:4961-70.
4. Oldach *et al.* Randomized, double-blind, multicenter phase 2 study comparing the efficacy and safety of oral solithromycin (CEM-101) to those of oral levofloxacin in the treatment of patients with community-acquired bacterial pneumonia. Antimicrob Agents Chemother. 2013;57:2526-34

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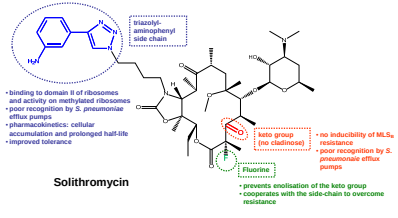
Background and Aims

Streptocccus pneumoniae is a main causative pathogen in CABP and in acute exacerbations of chronic bronchitis (AECB).

Because of increasing emergence of resistance to first and even second line antibiotics commonly recommended in these indications [1], discovery and clinical development of antibiotics active against these resistant strains is essential.

While telithromycin (the first approved ketolide) has represented a step forward in this context, its use has been hampered by the observation of unacceptable toxicities [2].

Solithromycin (SOL [3]) is a new generation of ketolides in which the intrinsic activity of telithromycin against macrolide-resistant isolates has been enhanced. It showed a favourable safety profile *vs.* levofloxacin in phase 2 trial of CABP [4] and has now entered phase 3 trial in comparison with moxifloxacin.



Solithromycin

Our aim was to assess the activity of SOL against a large collection of Belgian and German *S. pneumoniae* isolates enriched in strains with resistance against commonly recommended first and second line antibiotics. Ceftaroline (CPT) was added as it has been recently approved for CABP.

Methods

Isolates

Non-duplicate *S. pneumoniae* isolates (n=425) were selected from patients with respiratory tract infections (mainly bacterial exacerbations of chronic bronchitis and community acquired pneumonia) and with suspicion of MICs for macrolides, β-lactams, and/or fluoroquinolones close to or above the EUCAST breakpoints.

MICs

MICs were determined in cation-adjusted Mueller-Hinton broth supplemented with horse blood, using the S. pneumoniae strain ATCC 49619 as control and re-identification of each isolate by the optochin test.

Analyses

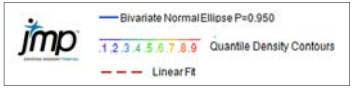
Data were first manually analyzed for basic statistics and susceptibility/resistance patterns (EUCAST interpretative criteria). For NS and R isolates, cross-resistance with SOL was assessed by linear fit, bivariate normal ellipse analysis (0.95 overlap), and quantile density contour coincidence (QDCI; 0.1 to 0.9) using JMP software (version 10.0.2).

Results

Table 1: Susceptibility testing and resistance correlation for NS and R isolates

Isolates		MIC (mg/L)						
		SOL	PEN	AMX	CRO	MXF	LVX	CPT
A. All isolates (n)		423	426	426	418	425	424	425
MIC (mg/L)	min	0.0018	0.0002	0.0039	0.0039	0.0039	0.0078	0.0005
	geom. mean	0.0229	0.0481	0.0726	0.0609	0.2279	1.4470	0.0252
	90%	0.062	2	2	1	2	8	0.25
	max	1	64	64	8	128	128	8
B. NS or R [a] isolates (n)			116 [b]	80 [b]	60 [b]	65 [b]	57 [b]	19 [b]
MIC (mg/L)	geom. mean	0.0434 [c]	1.1542	2.5713	1.3360	3.7123	15.615	0.9642
	90%	0.25 [c]	4	8	2	16	32	2
correlation [d]	alpha [e]		0.19	0.06	0.01	0.31	0.33	-0.54
	R^2 [f]		0.03	0.002	0.00019	0.1	0.05	0.092
	prob. > F [g]		0.04 *	0.68	0.97	0.008	0.070	0.207

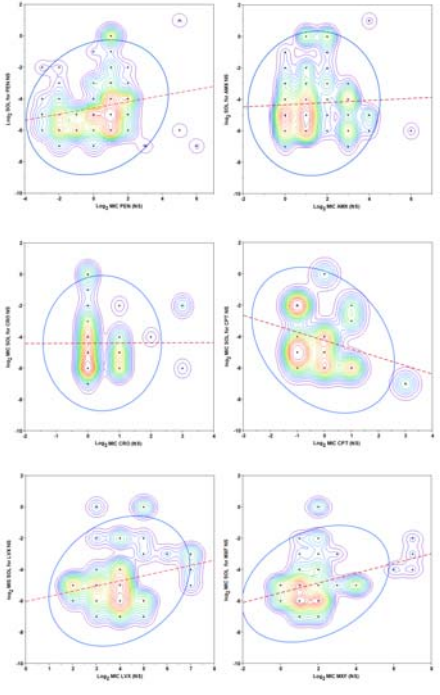
[a] EUCAST S breakpoints (mg/L): PEN > 0.06; AMX > 0.5; CRO > 0.5; MXF > 0.5; LVX > 2; CPT > 0.25 (http://www.eucast.org); not applicable for solithromycin
[b] isolates with NS or R phenotype to the corresponding antibiotic
[c] for strains with a NS or R phenotype to PEN
[d] correlations SOL (y) vs. each other antibiotic (x)
[e] from equation: SOL MIC = alpha x (comparator MIC) + b
[f] coefficient of determination
[g] p-value for "Lack of Fit" test.



Main observations

1. SOL MICs are low for all strains included in this collection;
2. Correlation and contour interval analysis performed with strains non-susceptible or resistant to the other antibiotics show that SOL MICs are not correlated with the MICs of these antibiotics

Figure 1: Correlation and contour interval analysis (NS strains)



Conclusions

- SOL maintains low MICs for clinical isolates with NS and R phenotypes to currently used or recently approved antibiotics for treatment of CABP
- There is no statistically-significant correlation (except for MXF and, to some extent, for PEN, but with a low angular coefficient [negative for ceftaroline] between MICs of SOL and those of the other antibiotics when considering strains non-susceptible or resistant these antibiotics
- SOL may, therefore, stand as a potentially useful alternative in environments where 1st or 2d line antibiotics can no longer be recommended.

This poster will be made available after the meeting at http://www.facm.ucl.ac.be/posters