P1641

Abstract (poster session)

The fluorocycline TP-271 is potent against major complicated community-acquired bacterial pneumonia (CABP) pathogens

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Objective: TP-271 is a novel, fully synthetic fluorocycline antibiotic in preclinical development for IV/oral treatment of respiratory infections caused by susceptible and multidrug-resistant (MDR) public health and biothreat pathogens. Method: In vitro susceptibility testing against recent isolates of Streptococcus spp., Staphylococcus aureus, Haemophilus influenzae, Moraxella catarrhalis and Mycoplasma pneumoniae was performed according to CLSI guidelines. TP-271 was tested against a total of 70 Legionella pneumophila isolates including serogroups 1 – 6 by agar dilution using buffered yeast extract agar. For Chlamydia pneumoniae, the minimal inhibitory concentration (MIC) was assessed in HEp-2 cell line without passage and was defined as the lowest concentration of test compound that resulted in reduction of inclusions. Time-kill assays with 3 to 4 clinical isolates per organism were performed as per CSLI guidelines in cation-adjusted Mueller Hinton broth (caMHB; S. aureus, M. catarrhalis), caMHB + 5% lysed horse blood (Streptococcus spp.), or Haemophilus Test Medium (H. influenzae). Results: TP-271 showed good activity against all respiratory pathogens, including atypical organisms L. pneumophila, C. pneumoniae and M. pneumoniae (Table). MIC90 values for TP-271 were 0.03 ug/mL for all streptococci, regardless of resistance phenotype. TP-271 was also active (MIC90 values 0.13 – 0.25 ug/mL) against methicillin-susceptible (MSSA) and -resistant (MRSA) S. aureus, including MRSA expressing Panton-Valentine Leukocidin (PVL) toxin. Against H. influenzae and M. catarrhalis¸TP-271 showed MIC90 values of 0.13 and <=0.016 ug/mL, respectively. At concentrations of 4X and 8X MIC, TP-271 was bacteriostatic with 3 of 4 S. pneumoniae isolates, all 3 S. pyogenes isolates, all 4 MRSA isolates, and all 3 M. catarrhalis isolates. TP-271 was bactericidal against all 3 H. influenzae isolates and at a top concentration of 2 ug/mL TP-271, bactericidal activity was seen against 1 of 3 S. pneumoniae, 2 of 3 S. pyogenes, 1 of 4 MRSA, all 3 H. influenzae, and all 3 M. catarrhalis isolates. Conclusions: TP-271 displayed excellent potency against major CABP pathogens and was unaffected by pre-existing tetracycline-specific, quinolone-resistant, or macrolide-resistant drug resistance phenotypes. TP-271 was also found to be bactericidal against some CABP isolates, particularly at 2 ug/mL. TP-271 shows promise as a new antibiotic for the treatment of complicated CABP.

Organism	N	MIC_{50}/MIC_{90} (range)						
		TP-271	Tetracycline[l]	Tigecycline	Macrolide[a]	Fluoroquinolone[b]	Linezolid	Vancomycin
Streptococcus pneumoniae	267	≤0.016/0.03 (≤0.016-0.03)	32/>32[c] (≤0.016->32)	≤0.016/≤0.016[d] (≤0.016-≤0.016)	>32/>32 (≤0.016->32)	1/1 (0.25-32)	1/1[c] (0.13-2)	0.5/0.5[c] (≤0.016-0.5)
S. pneumoniae penicillin-R[m]	125	≤0.016/0.03 (≤0.016-0.03)	32/>32 (0.031->32)	≤0.016/≤0.016[e] (≤0.016-≤0.016)	>32/>32 (≤0.016->32)	1/1 (0.5-8)	1/1 (0.25-2)	0.5/0.5 (0.25-0.5)
S. pneumoniae macrolide-R	209	≤0.016/0.03 (≤0.016-0.03)	32/>32[f] (0.03->32)	≤0.016/≤0.016[h] (≤0.016-≤0.016)	>32/>32 (1->32)	1/1[g] (0.25-32)	1/1[f] (0.25-2)	0.5/0.5[f] (0.13-0.5)
Streptococcus pyogenes	100	≤0.016/0.03 (≤0.016-0.03)	0.5/>32 (0.13->32)	≤0.016/≤0.016[i] (≤0.016-0.063)	0.063/>32 (≤0.016->32)	0.5/1 (0.25-2)	1/2 (0.5-2)	0.5/0.5 (0.25-0.5)
Staphylococcus aureus	155	0.06/0.25 (≤0.03-1)	≤2/32 (0.063->32)	0.12/0.25 (≤0.016-0.5)	>4/>4 (0.25->4)	>4/>4 (≤0.13->4)	2/4 (0.5-64)	1/1 (≤0.5-8)
S. aureus (MRSA)	124	0.063/0.13 (≤0.016-1)	≤2-32 (0.063->32)	0.13/0.25 (≤0.016-0.5)	>4/>4 (0.25->4)	>4/>4 (≤0.13->4)	2/4 (1-64)	1/1 (≤0.5-8)
S. aureus (MRSA) PVL+	25	0.063/0.13 (0.063-0.13)	≤2/≤2 (≤2-16)	0.12/0.12 (0.063-0.25)	>4/>4 (1->4)	2/>4 (≤0.13->4)	2/2 (1-4)	1/1 (≤0.5-1)
S. aureus (MSSA)	31	0.12/0.25 (≤0.031-0.25)	≤2/≤2 (≤2-32)	0.12/0.25 (0.03-0.25)	1/>4 (0.5->4)	0.25/0.5 (≤0.13->4)	2/4 (0.5-4)	1/1 (≤0.5-1)
Haemophilus influenzae	65	0.031/0.13 (≤0.016-0.25)	0.5/4 (0.13-16)	0.063/0.25 (≤0.016-0.5)	8/8 (0.063-16)	≤0.016/0.031 (≤0.016-0.13)	8/16 (4-32)	>32/>32[j] (16->32)
Moraxella catarrhalis	57	≤0.016/≤0.016 (≤0.016-0.031)	0.5/32 (0.13->32)	≤0.016/0.031 (≤0.016-0.13)	0.063/0.25 (≤0.016-4)	0.031/0.063 (0.031-0.13)	8/8 (2-32)	>32/>32[k] (16->32)
Legionella pneumophila	*70*	0.25/1 (≤0.004-2)	4/8 (0.5-8)	ND	0.25/0.5 (0.06-1)	ND	ND	ND
Chlamydia pneumoniae	10	4/4 (2-4)	0.25/0.25 (0.13-0.25)	ND	0.25/0.25 (0.13-0.25)	ND	ND	ND
Mycoplasma pneumoniae	20	0.001/0.004 (0.0005-0.008)	0.063/0.13 (0.032-0.13)	0.032/0.032 (0.016-0.125)	0.000063/8 (0.000032-16)	0.5/0.5 (0.25-0.5)	ND	ND

[a]erythromycin, azithromycin or clarithromycin; [b]ciprofloxacin or levofloxacin; [c]256 *S. pneumoniae* isolates; [d]137 S. pneumoniae isolates; [e]58 S. pneumoniae isolates; [f]201 *S. pneumoniae* isolates; [g]185 *S. pneumoniae* isolates; [h]82 *S. pneumoniae* isolates; [i]64 *S. pyogenes* isolates; [j]51 *H. influenzae* isolates; [k]43 *M. catarhalis* isolates ; [l] doxycycline for *C. pneumoniae* and *M. pneumoniae*; [m]penicillin MIC ≥2 µg/ml