

P1452

Abstract (poster session)

The novel isoindoline-containing pentacycline TP-834 is active against community and biothreat respiratory pathogens, and problematic Gram-positive pathogens

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Objective: TP-834 is a novel, fully-synthetic IV/oral pentacyclic antibiotic. TP-834 was selected from over 2000 analogs on the basis of its potency and spectrum, especially against multidrug-resistant (MDR) pathogens implicated in community-acquired bacterial pneumonia (CABP) and problematic Gram-positive infections. The goal of these studies was to profile the potency and spectrum of activity of TP-834 against panels of recent clinical isolates. Methods: Using standard CLSI methodology, TP-834 and clinical comparators were tested against recent clinical isolates and laboratory *Escherichia coli* strains recombinantly expressing individual tetracycline resistance genes: tet(A), tet(B), tet(M), tet(K) and tet(X). The anti-translation activity of TP-834 was confirmed in an *E. coli* in vitro coupled transcription/translation (TNT) assay in the presence and absence of purified Tet(M) protein. Results: TP-834 showed good antimicrobial potency against key MDR Gram-positive and Gram-negative pathogens responsible for CABP and skin infections, with representative MIC₉₀ values of 1, 0.5, 1, 0.5, 0.12, 1 and 0.25 mcg/mL for MRSA (n=99, including PVL+), MSSA (n=50), *Enterococcus faecalis* (n=157, including VRE), *Enterococcus faecium* (n=116, including VRE), *Streptococcus pneumoniae* (n=118, including penicillin- and macrolide-resistant), *Haemophilus influenzae* (n=64) and *Moraxella catarrhalis* (n=64). The MIC of TP-834 (1 mcg/ml) against a laboratory strain of *E. coli* was unaffected, or minimally affected, by expression of common tetracycline-resistance genes (≤ 4 -fold shift in MIC), as compared to that of tetracycline (MIC=2 mcg/ml; ≥ 64 -fold shift in MIC with expression of tetracycline resistance genes). The IC₅₀ of TP-834 in the TNT assay was 0.85 mcg/ml and was unaffected by the addition of purified Tet(M). Conclusions: TP-834 shows excellent potency against key MDR community respiratory and problematic Gram-positive pathogens, including those with common tetracycline-resistant mechanisms. TP-834 shows promise as an IV/oral agent for the treatment of complicated community CABP and infections due to MDR Gram-positive organisms.

Organism	N	MIC50/MIC90 (mcg/mL)						
		TP-834	TET	TGC	MACRO	LVX	LZD	VAN
<i>Streptococcus pneumoniae</i>	118	0.06/0.12	1/32	0.06/0.06	>4/>4	0.5/1	1/1	0.25/0.5
<i>Streptococcus pneumoniae</i> pen-R ^a	58	0.06/0.12	16/32	0.06/0.06	>4/>4	0.5/1	1/1	0.25/0.5
<i>S. pneumoniae</i> mac-R ^b	75	0.06/0.12	16/32	0.06/0.06	>4/>4	1/1	1/1	0.25/0.5
<i>Streptococcus pyogenes</i>	64	0.12/0.25	0.25/32	0.06/0.06	0.12/>4	0.5/1	1/1	0.5/0.5
<i>Streptococcus agalactiae</i>	50	0.5/0.5	32/>32	0.12/0.12	0.06/>4	0.5/1	1/1	0.5/0.5
<i>Streptococcus anginosus</i>	42	0.12/0.5	0.5/>16	0.016/0.06	0.06/>16	0.5/1	1/2	0.5/1
<i>Streptococcus intermedius</i>	30	0.12/0.12	0.25/>4	0.03/0.12	0.06/>0.5	1/2	1/1	0.5/0.5
<i>Streptococcus mitis</i>	29	0.06/0.25	0.5/>4	0.03/0.12	>0.5/>0.5	1/2	1/1	0.5/0.5
<i>Streptococcus sanguis</i>	18	0.06/0.12	0.25/2	0.03/0.06	0.03/>0.5	0.5/2	0.5/1	0.5/1
<i>Staphylococcus aureus</i> (MRSA)	99	0.5/1	0.25/>32 ^d	0.13/0.25	>4/>64 ^c	4/>32	2/4	1/1
<i>S. aureus</i> (MRSA) PVL ⁺	30	0.25/0.25	0.25/0.25	0.12/0.12	>4/>4	0.25/>2	1/2	1/1
<i>S. aureus</i> (MSSA)	50	0.25/0.5	0.25/0.5	0.12/0.25	2/>4	0.25/1	2/4	1/1
<i>Coagulase-negative Staphylococcus</i>	88	0.25/1	0.5/1	0.12/0.25	>4/>4	0.5/>4	1/2	1/2
<i>Enterococcus faecalis</i>	157	0.5/1	>32/>32	0.06/0.12	>4/>4 ^e	>4/>32	2/2	2/>32
<i>E. faecalis</i> (VRE)	64	0.5/1	>32/>32	0.06/0.12	>4/>4 ^f	>4/>32	2/2	>16/>32
<i>E. faecalis</i> (VSE)	93	0.5/1	>32/>32	0.06/0.12	>4/>4 ^g	1/>32	2/4	1/2
<i>Enterococcus faecium</i>	116	0.12/0.5	0.25/>32	0.06/0.12	>4/>4 ^h	>4/>32	2/4	>16/>32
<i>E. faecium</i> (VRE)	65	0.12/1	0.5/>32	0.06/0.13	>4/>4 ⁱ	>4/>32	2/4	>16/>32
<i>E. faecium</i> (VSE)	51	0.12/0.5	0.25/>32	0.06/0.06	>4/>4 ⁱ	>4/>4	2/2	0.5/1
<i>Haemophilus influenzae</i>	64	0.5/1	0.5/4	0.12/0.25	1/4	0.03/0.03	ND	ND
<i>Moraxella catarrhalis</i>	64	0.13/0.25	0.25/0.5	0.06/0.06	≤0.13/0.13	0.06/0.06	ND	ND

TET=tetracycline; TGC = tigecycline; MACRO=azithromycin or erythromycin; LVX=levofloxacin; LZD = linezolid; VAN= vancomycin; PEN=penicillin; ND = not done; ^apenicillin MIC ≥2 mcg/ml; ^b mac-R=macrolide-resistant; ^c 82 isolates; ^d 94 isolates; ^e 101 isolates; ^f 48 isolates; ^g 53 isolates; ^h 100 isolates; ⁱ 50 isolates