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In Vitro Evaluation of TD-1792, a Novel Antimicrobic with Potent Gram-positive Activity

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ABSTRACT

Background: TD-1792 is a potent multivalent glycopeptide targeting both transpeptidation and transglycosylation primarily in Gram-positive (GP) bacteria. We present results from an evaluation of TD-1792 against recent clinical GP isolates, including resistant (R) subsets.

Methods: Susceptibility test methods were those of the CLSI (agar dilution for anaerobes, broth microdilution for all others) with medium variations as required. A collection of 550 strains was selected from international surveillance programs and specialized R collections: *S. aureus* (89 strains), coag.-negative staphylococci (61), *Enterococcus* spp. (78), streptococci (*S. pneumoniae*, 88; viridans group, 69; ß-haemolytic, 37), *Bacillus* spp. (BSP; 10), *Corynebacterium* spp. (CSP; 11), anaerobes (42), *H. influenzae* (HI; 25), *M. catarrhalis* (MCAT; 10), Enterobacteriaceae (20) and non-fermentative bacilli (10).

Results: TD-1792 displayed greatest activity against GP organisms, especially staphylococci (MIC_{90} values, 0.016 to 0.03 µg/ml), streptococci (≤0.001 to 0.06 µg/ml) and enterococci (0.03 to 0.25 µg/ml), but was also active against BSP (0.12 µg/ml), CSP (0.25 µg/ml) and GP anaerobes (0.5 µg/ml). This agent was inactive against most Gram-negative isolates (MIC_{90} values, ≥16 µg/ml) except for HI (MIC_{90}, 8 µg/ml; range, 2 to 8 µg/ml) and MCAT (MIC_{90}, 0.5 µg/ml; range, 0.06 to 0.5 µg/ml). TD-1792 was unaffected by co-existing oxacillin-R in staphylococci, vancomycin-R (VanB type) enterococci, penicillin- and/or fluoroquinolone-R in streptococci, and quinupristin/dalfopristin-R among several tested GP groups. TD-1792 was also active against 21 VISA/hVISA and 3 VRSA isolates (MIC range, 0.03 to 0.25 µg/ml).

Conclusions: TD-1792 displayed superior antimicrobial potency against GP pathogens, including emerging R subsets. This agent represents a novel addition to the antimicrobial armamentarium as shown by its unique activity, warranting further clinical development.

INTRODUCTION

Resistance emergence among Gram-positive pathogens producing skin and skin structure and respiratory tract infections is endemic in most geographic regions, with methicillin-resistant *Staphylococcus aureus* (MRSA) reaching prevalences of 75% in some hospitals and penicillin-resistant *Streptococcus pneumoniae* in excess of 60%. The resultant increased usage of glycopeptide antimicrobics likewise has driven an increase in resistance among enterococci to vancomycin and, while in its early phases, among staphylococci as well (vancomycin-intermediate *S. aureus* [VISA], heterogeneous-VISA [hVISA], and vancomycin-resistant *S. aureus* [VRSA]). There is a critical need for new agents that retain activity against such resistant strains, although few new agents are in development to address this need.

TD-1792 is one such new agent, characterized as a potent multivalent antimicrobial targeting both transpeptidation and transglycosylation reactions primarily in Gram-positive bacteria. A recent Phase II clinical trial of complicated skin and skin structure infections (CSSSI) found comparability between TD-1792 and "standard of care" in clinical cures and microbiological eradication. The objective of the current study was to examine the in vitro activity of TD-1792 and comparator agents tested against contemporary clinical isolates of Gram-positive bacteria (principally staphylococci, enterococci and streptococci, including rare resistant subsets) and Gram-negative respiratory tract pathogens (*Haemophilus influenza* and *Moraxella catarrhalis*) collected as part of longitudinal international surveillance protocols. A total of 550 strains were tested by reference methods of the Clinical and Laboratory Standards Institute (CLSI, formerly the NCCLS) with susceptibilities interpreted by current CLSI criteria.

MATERIALS AND METHODS

Bacterial strain collection: A collection of 550 strains was selected from international surveillance programs and specialized resistance organism collections: *S. aureus* (89 strains), coagulase-negative staphylococci (61), *Enterococcus* spp. (78), streptococci (*Streptococcus pneumoniae* [88]; viridans group [69]; ß-haemolytic [37]), *Bacillus* spp. (10), *Corynebacterium* spp. (11), anaerobes (42), *Haemophilus influenzae* (25), *Moraxella catarrhalis* (10), Enterobacteriaceae (20) and non-fermentative Gram-negative bacilli (10). Characteristics of all tested isolates, including resistant subsets, are found in Table 1.

Susceptibility test methods: The CLSI broth microdilution method (M7-A7 [2006]) with appropriate medium variations (cation-adjusted Mueller-Hinton broth with added 2 - 5% lysed horse blood for testing of streptococci; HTM medium for testing of *H. influenzae*; supplementation with 50 mg/L calcium for testing daptomycin) was used for testing of aerobic and facultative species; and the CLSI reference agar dilution method (M11-A7 [2007]) was used for the testing of anaerobes. Quality control (QC) included daily testing of CLSI recommended QC strains: *E. coli* ATCC 25922 and 35218, *S. aureus* ATCC 25923 and 29213, *E. faecalis* ATCC 29212, *P. aeruginosa* ATCC 27853, *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247 and 49766, *Bacteroides fragilis* ATCC 25285, *B. thetaiotaomicron* ATCC 29741 and *Eubacterium lentum* ATCC 43055. Only results with concurrent acceptable QC values were included in this study presentation.

RESULTS

- TD-1792 displayed broad-spectrum activity and potency against the Gram-positive pathogens tested as part of this study (Table 1), including (MIC_{90}) staphylococci (0.016 to 0.03 µg/ml), streptococci (≤0.001 to 0.06 µg/ml) and vancomycin-susceptible enterococci (0.016 to 0.25 µg/ml), but was equally active against rarer pathogens such as *Bacillus* spp. (0.12 µg/ml), *Corynebacterium* spp. (0.25 µg/ml), and Gram-positive anaerobes (0.5 µg/ml).
- This agent was inactive against most Gram-negative isolates tested including the Enterobacteriaceae, non-fermentative Gram-negative bacilli and anaerobic bacilli (MIC_{90} values, ≥16 µg/ml).
- TD-1792 had limited activity against *H. influenzae* (MIC_{90}, 8 µg/ml; range, 2 to 8 µg/ml).
- TD-1792 was found to be active against *M. catarrhalis* isolates (MIC_{90} value, 0.5 µg/ml; range, 0.06 to 0.5 µg/ml) with MIC results comparable to those of Gram-positive cocci.
- The TD-1792 MIC_{90} value against MRSA isolates was two-fold higher than for MSSA isolates (MIC_{90} of 0.03 and 0.016 µg/ml, respectively). Penicillin resistance in streptococci was associated with a four-fold increase in MIC_{90} values. All penicillin-resistant streptococci were inhibited by ≤0.03 µg/ml of TD-1792.
- Most notable decreases in TD-1792 potency were seen in vancomycin-resistant enterococci (MIC_{50} values, eight-fold higher in *E. faecalis* and two-fold higher in *E. faecium*). Potency against hVISA and VRSA was also decreased (four- and eight-fold, respectively) although all strains were inhibited by ≤0.25 µg/ml of TD-1792.

Table 1. Cumulative frequency distributions of 34 organism groups (including resistant subsets) when tested against TD-1792 (550 strains).

	MIC (µg/ml)		Cumulative % inhibited at MIC (µg/ml)														
Organism (no. tested)	50%	90%	≤0.001	0.002	0.004	0.008	0.016	0.03	0.06	0.12	0.25	0.5	1	2	4	8	≥16
S. aureus																	
Oxacillin-S (26)	0.016	0.016	0	23	31	31	92	100	-	-	-	-	-	-	-	-	-
Oxacillin-R (25)	0.03	0.03	0	0	0	0	36	92	100	-	-	-	-	-	-	-	-
Coagulase-negative staphylococci																	
Oxacillin-S (25)	0.016	0.016	8	28	40	40	92	100	-	-	-	-	-	-	-	-	-
Oxacillin-R (25)	0.03	0.03	0	4	4	4	32	100	-	-	-	-	-	-	-	-	-
E. faecalis																	
Vancomycin-S (11)	0.002	0.03	45	54	54	64	82	100	-	-	-	-	-	-	-	-	-
Vancomycin-R (9)	0.016	-	22	33	33	44	67	67	78	78	78	78	78	89	89	100	-
E. faecium																	
Vancomycin-S (11)	0.03	0.25	18	27	27	27	45	54	73	82	91	100	-	-	-	-	-
Vancomycin-R (12)	0.06	0.25	8	17	17	17	42	42	75	83	92	92	92	92	100	-	-
Other *Enterococcus* spp. (10)	≤0.001	0.016	60	60	80	80	100	-	-	-	-	-	-	-	-	-	-
S. pneumoniae																	
Penicillin-S (25)	≤0.001	0.002	80	92	100	-	-	-	-	-	-	-	-	-	-	-	-
Penicillin-I (15)	≤0.001	0.008	53	80	87	93	100	-	-	-	-	-	-	-	-	-	-
Penicillin-R (14)	0.002	0.008	14	57	86	100	-	-	-	-	-	-	-	-	-	-	-
Multidrug-R (22)	0.004	0.016	9	36	54	77	100	-	-	-	-	-	-	-	-	-	-
Viridans group streptococci																	
Penicillin-S (20)	≤0.001	0.008	70	85	85	100	-	-	-	-	-	-	-	-	-	-	-
Penicillin-I (19)	0.002	0.06	42	53	63	63	74	84	95	100	-	-	-	-	-	-	-
Penicillin-R (15)	0.008	0.03	27	40	40	60	87	100	-	-	-	-	-	-	-	-	-
ß-haemolytic streptococci (31)	≤0.001	≤0.001	93	93	97	100	-	-	-	-	-	-	-	-	-	-	-
Bacillus spp. (10)	0.06	0.12	0	0	10	10	30	30	70	90	100	-	-	-	-	-	-
Corynebacterium spp. (11)	0.03	0.25	0	0	0	0	27	54	54	72	91	100	-	-	-	-	-
Levofloxacin-resistant streptococci (26)[a]	≤0.001	0.008	69	73	88	96	100	-	-	-	-	-	-	-	-	-	-
Quinupristin/Dalfopristin resistant																	
S. aureus (10)	0.016	0.03	0	10	10	10	70	100	-	-	-	-	-	-	-	-	-
Coagulase-neg staphylococci (10)	0.016	0.03	0	30	30	30	80	100	-	-	-	-	-	-	-	-	-
Streptococci (6)[b]	≤0.001	-	100	-	-	-	-	-	-	-	-	-	-	-	-	-	-
E. faecium (11)	0.016	0.06	45	45	45	45	55	73	100	-	-	-	-	-	-	-	-
Linezolid-resistant																	
Gram-positive (14)[c]	0.03	0.25	7	21	36	36	43	79	86	86	100	-	-	-	-	-	-
VISA/hVISA (21)	0.06	0.12	0	0	0	0	0	43	76	95	100	-	-	-	-	-	-
VRSA (3)	0.12	-	0	0	0	0	0	0	0	67	100	-	-	-	-	-	-
H. influenzae																	
ß-lactamase negative (14)	4	8	0	0	0	0	0	0	0	0	0	0	0	28	86	100	-
ß-lactamase positive (11)	4	8	0	0	0	0	0	0	0	0	0	0	0	0	66	100	-
M. catarrhalis (10)	0.25	0.5	0	0	0	0	0	0	10	30	80	100	-	-	-	-	-
Enterobacteriaceae (20)	≥16	≥16	0	0	0	0	0	0	0	0	0	0	0	0	5	30	100
Non-fermentative bacilli (10)	≥16	≥16	0	0	0	0	0	0	0	0	0	0	10	20	20	30	100
Anaerobes																	
Gram-positive (19)	0.03	0.5	NT[d]	NT	NT	21	31	53	53	63	89	100	-	-	-	-	-
Gram-negative (23)	≥16	≥16	NT	NT	NT	0	0	0	0	0	0	4	9	9	9	13	100

a. Isolates include *S. pneumoniae* (10), *S. mitis* (4), ß-haemolytic streptococci group B (4), viridans group streptococci (3), *S. intermedius* (1), *S. oralis* (1), *S. uberis* (1), ß-haemolytic streptococci group C (1), and ß-haemolytic streptococci group G (1).
b. Isolates include *S. pneumoniae* (2), *S. aeruginosa* (1), *S. mitis* (1), *S. uberis* (1), and viridans group streptococcus (1).
c. Isolates include *S. aureus* (4), *S. epidermidis* (1), *S. oralis* (1), *E. faecalis* (4), and *E. faecium* (4); vancomycin-resistant strains are excluded.
d. NT = Not tested.

- TD-1792 was unaffected by co-existing linezolid-resistance in staphylococci and enterococci. Linezolid-resistant strains were all inhibited by ≤0.25 µg/ml of TD-1792.

CONCLUSIONS

- TD-1792 is a new agent, characterized as a potent multivalent antimicrobial targeting both transpeptidation and transglycosylation reactions primarily in Gram-positive bacteria.
- All staphylococci, vancomycin-susceptible enterococci, streptococci, *Bacillus* spp., corynebacteria, anaerobic Gram-positive cocci and *M. catarrhalis* isolates were inhibited by ≤0.5 µg/ml of TD-1792.
- Vancomycin-resistant enterococci and *H. influenzae* were inhibited by ≤8 µg/ml of TD-1792.
- While TD-1792 displayed enhanced antimicrobial potency against most Gram-positive pathogens, decreases in potency were apparent in enterococci displaying decreased susceptibility to vancomycin.
- This Gram-positive-targeted agent represents a promising, potent addition to the existing antimicrobial armamentarium given its unique activity profile, MRSA potency and success in a recently conducted Phase II CSSSI trial, warranting further development.

SELECTED REFERENCES

1. Chambers HF (2005). Community-associated MRSA--resistance and virulence converge. *N Engl J Med* 352: 1485-1487.
2. Cosgrove SE, Qi Y, Kaye KS, Harbarth S, Karchmer AW, Carmeli Y (2005). The impact of methicillin resistance in *Staphylococcus aureus* bacteremia on patient outcomes: mortality, length of stay, and hospital charges. *Infect Control Hosp Epidemiol* 26: 166-174.
3. Clinical and Laboratory Standards Institute. (2007). *Performance standards for antimicrobial susceptibility testing, 17th informational supplement M100-S17*. Wayne, PA: CLSI.
4. Clinical and Laboratory Standards Institute. (2006). *Approved Standard M7-A7: Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically, 7th Ed*. Wayne, PA: CLSI.
5. Jacobs MR, Felmingham D, Appelbaum PC, Gruneberg RN (2003). The Alexander Project 1998-2000: Susceptibility of pathogens isolated from community-acquired respiratory tract infection to commonly used antimicrobial agents. *J Antimicrob Chemother* 52: 229-246.
6. Johnson DM, Stilwell MG, Fritsche TR, Jones RN (2006). Emergence of multidrug-resistant *Streptococcus pneumoniae*: Report from the SENTRY Antimicrobial Surveillance Program (1999-2003). *Diagn Microbiol Infect Dis* 56: 69-74.
7. Klugman KP (2007). Clinical impact of antibiotic resistance in respiratory tract infections. *Int J Antimicrob Agents* 29 Suppl 1: S6-10.
8. NNIS (1999). National Nosocomial Infections Surveillance (NNIS) System Report, Data Summary from January 1990-May 1999, Issued June 1999. *Am J Infect Control* 27: 520-532.
9. Wilson MA (2003). Skin and soft-tissue infections: impact of resistant gram-positive bacteria. *Am J Surg* 186: 35S-41S; discussion 42S-43S, 61S-64S.