Antimicrobial Activity of PTK 0796 (Omadacycline) Tested against Gram-positive Organisms Isolated from European Hospitals in 2011

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Amended Abstract

Objective: To evaluate the activity of PTK 0796 (PTK) against Gram-positive (GP) cocci causing infections in European (EU) hospitals. PTK (7-dimethylamino, 9-[2,2-dimethyl-propyl]-aminomethylcycline) is a novel antibacterial agent of the tetracycline family, which is under clinical development (IV and oral formulations).

Methods: 2719 strains from 25 medical centers in 10 EU countries, Turkey and Israel were collected in 2011 and tested for susceptibility (S) against PTK, tigecycline (TIG) and many other comparators by CLSI broth microdilution methods. MIC results were interpreted according to EUCAST and CLSI breakpoint criteria. The isolates were collected mainly from skin/skin structure infections, bacteremia and pneumonia, and include *S. aureus* (1,572; 27.4% oxacillin-resistant [MRSA]), coagulase-negative staphylococci (CoNS; 344, 71.5% oxacillin-resistant [R]), *E. faecalis* (EF; 270; 0.7% vancomycin [VAN]-R [MIC, ≥8 mg/L]), *E. faecium* (EFM; 156; 23.7% VAN-R), β-haemolytic streptococci (βHS; 245) and viridans group streptococci (VGS; 132).

Results: PTK was very active against oxacillin-S *S. aureus* (MSSA) and MRSA with a MIC_{90} of 0.12 and 0.25 mg/L respectively (see Table 2). PTK activity against *S. aureus* was eight-fold greater than linezolid and VAN, two-fold greater than daptomycin and similar to TIG. MRSA rates varied from 1.0% in Sweden to 61.5% in Portugal (27.4% overall). The highest PTK MIC value among *S. aureus* was only 2 mg/L and >99% of strains were inhibited at PTK MIC of ≤0.25 mg/L. CoNS exhibited slightly higher PTK MICs ($MIC_{50/90}$, 0.12/1 mg/L) compared to *S. aureus*, with a bimodal distribution. EF ($MIC_{50/90}$, 0.12/0.25 mg/L) and EFM ($MIC_{50/90}$, 0.06/0.12 mg/L) were very S to PTK and VAN R did not adversely affect PTK activity against enterococci. VAN-R EFM was detected in 10 of 12 countries, while VAN-R EF was observed only in Germany and Italy (one strain each). βHS and VGS exhibited very low PTK MIC values ($MIC_{50/90}$, 0.06/0.12 mg/L for all groups).

Conclusions: PTK demonstrated potent activity against a large collection of contemporary (2011) GP clinical isolates. Its activity was similar to that of TIG and was not affected by R to other antimicrobial classes.

Introduction

PTK 0796 (omadacycline), is a novel antibacterial agent of the tetracycline family, which is currently under clinical development as both intravenous and oral formulations. This new tetracycline has shown broad-spectrum activity and efficacy in animal models for treating clinically prevalent infections caused by Gram-positive, Gram-negative, atypical and anaerobic bacteria, including those with multi-drug resistance (MDR).

Gram-positive bacteria, especially staphylococci, β-haemolytic streptococci and enterococci, are extremely common and important pathogens causing serious infections in the hospital environment. *Staphylococcus aureus* represents the main cause of acute bacterial skin and skin structure infections (ABSSSI) and bloodstream infections (BSI), with methicillin-resistant strains (MRSA) accounting for approximately 50% of *S. aureus.* β-haemolytic streptococci (dominantly *Streptococcus pyogenes* and *S. agalactiae*) also represent important causes of ABSSSI; while coagulase-negative staphylococci (CoNS) and enterococci, along with *S. aureus,* are responsible for approximately one-half of all BSI. In this report, we evaluated the activity of PTK 0976 tested by reference methods against Gram-positive cocci causing infections in European (EU) hospitals.

Materials and Methods

Organism collection: A total of 2719 strains from 25 medical centers in 10 EU countries, Turkey and Israel were collected in 2011. The isolates were collected mainly from ABSSSI, BSI and pneumonia, and included *S. aureus* (1,572; 27.4% oxacillin-resistant [MRSA]), CoNS (344, 71.5% oxacillin-resistant), *E. faecalis* (270; 0.7% vancomycin-resistant [MIC, ≥8 mg/L]), *E. faecium* (156; 23.7% vancomycin-resistant), β-haemolytic streptococci (245) and viridans group streptococci (132).

Susceptibility testing: Isolates were tested by Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (M07-A9; 2012) using validated dry-form panels produced by ThermoFisher Scientific, formerly TREK Diagnostics Systems/Sensititre (Cleveland, Ohio, USA). Interpretive breakpoint criteria for comparator agents were those published in CLSI (M100-S22; 2012) and European Committee on Antimicrobial Susceptibility Testing (EUCAST, 2012), except for tigecycline where the United States Food and Drug Administration (USA-FDA) breakpoints were applied (Tygacil Package Insert, 2010). Validation of the minimum inhibitory concentration (MIC) values was performed by concurrent testing of CLSI-recommended (M100-S22, 2012) quality control (QC) strains: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212 and *Streptococcus pneumoniae* ATCC 49619; and all QC results were within published limits. MIC ranges for PTK 0796 and comparator agents tested against ATCC QC strains were those published in the CLSI M100-S22 (2012).

Results

- PTK 0796 (omadacycline) was very active when tested against oxacillin-susceptible *S. aureus* (MSSA) and MRSA with a MIC_{90} of 0.12 and 0.25 mg/L respectively (Tables 1 and 2). The highest PTK 0796 MIC value among *S. aureus* was only 2 mg/L and 99.7% of strains were inhibited at a PTK 0796 MIC of ≤0.25 mg/L (Table 1).
- PTK 0796 ($MIC_{50/90}$, 0.12/0.12 mg/L) activity against *S. aureus* was eight-fold greater than those of linezolid ($MIC_{50/90}$, 1/2 mg/L) and vancomycin ($MIC_{50/90}$, 1/1 mg/L), respectively; two-fold greater than daptomycin ($MIC_{50/90}$, 0.25/0.5 mg/L) and similar to tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), see Table 2.
- MRSA rates varied across EU from only 1.0% in Sweden to 61.5% in Portugal (27.4% overall). The most active agents against MRSA were PTK 0796 ($MIC_{50/90}$, 0.12/0.25 mg/L) and tigecycline ($MIC_{50/90}$, 0.06/0.12 mg/L), see Table 2.
- CoNS exhibited slightly higher PTK 0796 MIC values ($MIC_{50/90}$, 0.12/1 mg/L) compared to *S. aureus*, with a bimodal distribution (Tables 1 and 2).
- *E. faecalis* ($MIC_{50/90}$, 0.12/0.25 mg/L) and *E. faecium* ($MIC_{50/90}$, 0.06/0.12 mg/L) were very susceptible to PTK 0796, and resistance to vancomycin did not adversely affect PTK 0796 activity against these organisms (Tables 1 and 2).
- Vancomycin-resistant *E. faecium* was detected in 10 of 12 countries (23.7% overall), while vancomycin-resistant *E. faecalis* (0.7% overall) was observed only in Germany and Italy (one strain each).
- β-haemolytic streptococci and viridans group streptococci exhibited very low PTK 0796 MIC values ($MIC_{50/90}$, 0.06/0.12 mg/L for all groups).

Conclusions

- PTK 0796 (omadacycline) demonstrated very potent activity when tested against a large collection of contemporary (2011) Gram-positive clinical isolates.
- PTK 0796 activity was similar to that of tigecycline and was not affected by resistance to other antimicrobial classes including tetracyclines.

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Table 2. Activity of PTK 0796 (omadacycline) and comparator antimicrobial agents when tested against isolates from European medical centers.

Antimicrobial agent (no. tested)	MIC (mg/L)			%Susc. / %Resistant	
	MIC_{50}	MIC_{90}	Range	CLSI[a]	EUCAST[a]
S. aureus (1,572)					
PTK 0796	0.12	0.12	≤0.015 – 2	- / -	- / -
Tigecycline[b]	0.06	0.12	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Oxacillin	0.5	>2	≤0.25 – >2	72.5 / 27.5	72.5 / 27.5
Doxycycline	0.12	0.25	≤0.06 – >8	98.0 / 0.4	95.2 / 2.9
Tetracycline	≤0.25	0.5	≤0.25 – >8	93.9 / 5.6	93.4 / 6.4
Erythromycin	0.25	>16	≤0.12 – >16	70.5 / 27.2	70.7 / 28.5
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	91.8 / 8.1	91.3 / 8.2
Levofloxacin	0.25	>4	≤0.12 – >4	71.9 / 27.3	71.9 / 27.3
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >4	99.1 / 0.9	99.1 / 0.8
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	99.9 / 0.1
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
MSSA (1,140)					
PTK 0796	0.12	0.12	≤0.015 – 0.5	- / -	- / -
Tigecycline[b]	0.06	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Doxycycline	0.12	0.12	≤0.06 – >8	99.3 / 0.2	96.8 / 1.2
Tetracycline	≤0.25	≤0.25	≤0.25 – >8	95.9 / 3.8	95.4 / 4.5
Erythromycin	0.25	>16	≤0.12 – >16	84.6 / 13.7	84.6 / 14.9
Telithromycin	≤0.06	0.12	≤0.06 – >8	97.7 / 2.1	- / -
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	97.9 / 2.0	97.5 / 2.1
Levofloxacin	≤0.12	0.25	≤0.12 – >4	94.8 / 4.7	94.8 / 4.7
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >4	99.6 / 0.4	99.6 / 0.4
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
MRSA (432)					
PTK 0796	0.12	0.25	0.03 – 2	- / -	- / -
Tigecycline[b]	0.06	0.12	≤0.03 – 0.5	100.0 / -	100.0 / 0.0
Doxycycline	0.12	1	≤0.06 – >8	94.7 / 0.9	91.0 / 7.4
Tetracycline	≤0.25	>8	≤0.25 – >8	88.7 / 10.4	88.2 / 11.6
Erythromycin	>16	>16	≤0.12 – >16	33.6 / 62.7	34.0 / 64.4
Telithromycin	≤0.06	>8	≤0.06 – >8	76.4 / 23.4	- / -
Clindamycin	≤0.25	>2	≤0.25 – >2	75.7 / 24.3	75.0 / 24.3
Levofloxacin	>4	>4	≤0.12 – >4	11.6 / 86.8	11.6 / 86.8
Linezolid	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
TMP/SMX[c]	≤0.5	≤0.5	≤0.5 – >4	97.9 / 2.1	97.9 / 1.9
Teicoplanin	≤2	≤2	≤2 – 4	100.0 / 0.0	99.8 / 0.2
Vancomycin	1	1	0.5 – 2	100.0 / 0.0	100.0 / 0.0
Daptomycin	0.25	0.5	0.12 – 1	100.0 / -	100.0 / 0.0
CoNS (344)					
PTK 0796	0.12	1	≤0.015 – 2	- / -	- / -
Tigecycline[b]	0.06	0.12	≤0.03 – 0.5	- / -	100.0 / 0.0
Oxacillin	>2	>2	≤0.25 – >2	28.5 / 71.5	28.5 / 71.5
Doxycycline	0.25	4	≤0.06 – >8	93.6 / 1.2	85.1 / 10.2
Tetracycline	0.5	>8	≤0.25 – >8	82.3 / 16.3	69.2 / 21.5
Erythromycin	>16	>16	≤0.12 – >16	37.5 / 62.2	37.5 / 62.2
Telithromycin	≤0.06	>8	≤0.06 – >8	79.1 / 20.6	- / -
Clindamycin	≤0.25	>2	≤0.25 – >2	77.6 / 22.4	75.3 / 22.4
Levofloxacin	2	>4	≤0.12 – >4	45.1 / 49.7	45.1 / 49.7
Linezolid	0.5	1	0.25 – >8	99.1 / 0.9	99.1 / 0.9
TMP/SMX[c]	≤0.5	>4	≤0.5 – >4	62.5 / 37.5	62.5 / 21.5
Teicoplanin	≤2	8	≤2 – 16	97.1 / 0.0	87.2 / 12.8
Vancomycin	1	2	0.5 – 4	100.0 / 0.0	98.5 / 1.5
Daptomycin	0.25	0.5	≤0.06 – 2	99.7 / -	99.7 / 0.3
E. faecalis (270)					
PTK 0796	0.12	0.25	≤0.015 – 1	- / -	- / -
Tigecycline[b]	0.06	0.06	≤0.03 – 0.25	100.0 / -	100.0 / 0.0
Ampicillin	1	2	≤0.25 – 4	100.0 / 0.0	100.0 / 0.0
Doxycycline	8	>8	≤0.06 – >8	37.6 / 13.3	- / -
Tetracycline	>8	>8	≤0.25 – >8	25.8 / 74.2	- / -
Levofloxacin	1	>4	≤0.12 – >4	76.0 / 23.6	- / -
Linezolid	1	2	0.25 – 2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	2	0.5 – >16	99.3 / 0.7	99.3 / 0.7
Teicoplanin	≤2	≤2	≤2 – >16	99.3 / 0.7	98.9 / 1.1
Daptomycin	1	1	≤0.06 – 2	100.0 / -	- / -
E. faecium (156)					
PTK 0796	0.06	0.12	≤0.015 – 0.25	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ampicillin	>8	>8	0.5 – >8	5.8 / 94.2	5.1 / 94.2
Doxycycline	0.12	>8	≤0.06 – >8	71.8 / 17.3	- / -
Tetracycline	0.5	>8	≤0.25 – >8	56.4 / 42.9	- / -
Levofloxacin	>4	>4	1 – >4	7.1 / 90.4	- / -
Linezolid	1	1	0.25 – 8	98.1 / 1.9	98.1 / 1.9
Teicoplanin	≤2	>16	≤2 – >16	78.2 / 20.5	78.2 / 21.8
Vancomycin	1	>16	0.5 – >16	76.3 / 23.7	76.3 / 23.7
Daptomycin	2	2	0.12 – 4	100.0 / -	- / -
Vancomycin-susceptible (119)					
PTK 0796	0.06	0.12	≤0.015 – 0.25	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Ampicillin	>8	>8	0.5 – >8	7.6 / 92.4	6.7 / 92.4
Doxycycline	0.12	>8	≤0.06 – >8	74.8 / 18.5	- / -
Tetracycline	0.5	>8	≤0.25 – >8	58.8 / 40.3	- / -
Levofloxacin	>4	>4	1 – >4	9.2 / 87.4	- / -
Linezolid	1	1	0.25 – 8	99.2 / 0.8	99.2 / 0.8
Teicoplanin	≤2	≤2	≤2	100.0 / 0.0	100.0 / 0.0
Vancomycin	1	1	0.5 – 4	100.0 / 0.0	100.0 / 0.0
Daptomycin	2	2	0.12 – 4	100.0 / -	- / -
Vancomycin-non-susceptible (37)					
PTK 0796	0.06	0.12	0.03 – 0.12	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.06	100.0 / -	100.0 / 0.0
Ampicillin	>8	>8	>8	0.0 / 100.0	0.0 / 100.0
Doxycycline	2	>8	≤0.06 – >8	62.2 / 13.5	- / -
Tetracycline	>8	>8	≤0.25 – >8	48.6 / 51.4	- / -
Levofloxacin	>4	>4	>4	0.0 / 100.0	- / -
Linezolid	1	2	1 – 8	94.6 / 5.4	94.6 / 5.4
Teicoplanin	>16	>16	≤2 – >16	8.1 / 86.5	8.1 / 91.9
Vancomycin	>16	>16	>16	0.0 / 100.0	0.0 / 100.0
Daptomycin	2	2	0.5 – 4	100.0 / -	- / -
β-haemolytic streptococci[d] (245)					
PTK 0796	0.06	0.12	0.03 – 0.5	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.12	100.0 / -	100.0 / 0.0
Penicillin	≤0.06	≤0.06	≤0.06	100.0 / -	100.0 / 0.0
Doxycycline	0.25	>8	≤0.06 – >8	- / -	58.6 / 39.8
Tetracycline	0.5	>8	≤0.25 – >8	54.3 / 42.9	51.8 / 45.7
Levofloxacin	0.5	1	≤0.12 – >4	99.2 / 0.8	95.1 / 0.8
Linezolid	1	1	0.5 – 1	100.0 / -	100.0 / 0.0
Erythromycin	≤0.12	8	≤0.12 – >16	78.4 / 21.6	78.4 / 21.6
Clindamycin	≤0.25	≤0.25	≤0.25 – >2	90.6 / 9.4	90.6 / 9.4
Vancomycin	0.5	0.5	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	≤0.06	0.25	≤0.06 – 0.5	100.0 / -	100.0 / 0.0
Viridans group streptococci[e] (132)					
PTK 0796	0.06	0.12	≤0.015 – 1	- / -	- / -
Tigecycline[b]	≤0.03	0.06	≤0.03 – 0.25	100.0 / -	- / -
Penicillin	≤0.06	2	≤0.06 – >8	64.4 / 9.8	73.5 / 9.8
Doxycycline	0.25	>8	≤0.06 – >8	- / -	- / -
Tetracycline	0.5	>8	≤0.25 – >8	66.7 / 32.6	- / -
Levofloxacin	1	2	0.25 – >4	94.7 / 5.3	- / -
Linezolid	1	1	≤0.12 – 2	100.0 / -	- / -
Erythromycin	1	>16	≤0.12 – >16	47.0 / 53.0	- / -
Clindamycin	≤0.25	>2	≤0.25 – >2	80.3 / 19.7	80.3 / 19.7
Vancomycin	0.5	1	0.25 – 1	100.0 / -	100.0 / 0.0
Daptomycin	0.25	1	≤0.06 – 2	99.2 / -	- / -

a. Criteria as published by the CLSI [2012] and EUCAST [2012], β-lactam susceptibility should be directed by the oxacillin test results. "-" indicates that no breakpoint criteria has been established.
b. USA-FDA breakpoints were applied [Tygacil Product Insert, 2010].
c. TMP/SMX = trimethoprim/sulfamethoxazole.
d. Includes: *Streptococcus dysgalactiae* (7 strains), *Streptococcus equisimilis* (3 strains), Group A *Streptococcus* (85 strains), Group B *Streptococcus* (93 strains), Group C *Streptococcus* (15 strains), Group F *Streptococcus* (1 strain), and Group G *Streptococcus* (41 strains).
e. Includes: *Streptococcus anginosus* (13 strains), *S. bovis* (3 strains), *S. constellatus* (4 strains), *S. gallolyticus* (1 strain), *S. gordonii* (1 strain), *S. intermedius* (2 strains), *S. milleri* (3 strains), *S. mitis* (22 strains), *S. mutans* (1 strain), *S. oralis* (12 strains), *S. parasanguinis* (2 strains), *S. salivarius* (8 strains), *S. sanguinis* (9 strains), *S. suis* (1 strain), *S. vestibularis* (2 strains), unspeciated alpha-haemolytic streptococci (4 strains), and unspeciated viridans group streptococci (44 strains).

Table 1. PTK 0796 (omadacycline) MIC distributions when tested against bacterial isolates from European medical centers (2011).

Organism (no. tested)[a]	No. of isolates (cumulative %) inhibited at PTK 0796 MIC (mg/L) of:						
	≤0.03	0.06	0.12	0.25	0.5	1	2
S. aureus (1572)	13(0.8)	237(15.9)	1196(92.0)	121(99.7)	3(99.9)	1(99.9)	1(100.0)
MSSA (1140)	8(0.7)	183(16.8)	878(93.8)	68(99.7)	3(100.0)	-	-
MRSA (432)	5(1.2)	54(13.7)	318(87.3)	53(99.5)	0(99.5)	1(99.8)	1(100.0)
CoNS (344)	23(6.7)	117(40.7)	58(57.6)	34(67.4)	73(88.7)	37(99.4)	2(100.0)
E. faecalis (270)	25(9.3)	103(47.4)	94(82.2)	46(99.3)	1(99.6)	1(100.0)	-
E. faecium (156)	21(13.5)	105(80.8)	27(98.1)	3(100.0)	-	-	-
Vancomycin-susceptible (119)	19(16.0)	81(84.0)	16(97.5)	3(100.0)	-	-	-
Vancomycin-non-susceptible[b] (37)	2(5.4)	24(70.3)	11(100.0)	-	-	-	-
β-haemolytic streptococci (245)	56(22.9)	124(73.5)	50(93.9)	14(99.6)	1(100.0)	-	-
Viridans group streptococci (132)	32(24.2)	67(75.0)	23(92.4)	8(98.5)	1(99.2)	1(100.0)	-

a. MSSA=methicillin-susceptible *S. aureus*; MRSA=methicillin-resistant *S. aureus*; CoNS=coagulase-negative staphylococci.
b. Vancomycin MIC of ≥8 mg/L.