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ACTIVITY OF OMIGANAN AGAINST CONTEMPORARY (2005-2006) GRAM-POSITIVE PATHOGENS RESPONSIBLE FOR CATHETER COLONIZATION AND CATHETER-RELATED BLOODSTREAM INFECTIONS

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ABSTRACT

Background: Omiganan (OMI) is a rapidly cidal cationic peptide with a broad antimicrobial spectrum, including bacteria and fungi, and is currently in a Phase III clinical trial for topical use in prevention of catheter-associated infections (CAI). We present the spectrum of activity and potency of OMI and comparator agents against a contemporary (2005-2006) collection of GP isolates.

Methods: 390 clinical isolates collected from USA medical centers were susceptibility (S) tested against OMI and 11 comparator agents by CLSI broth microdilution methods. Isolates originated from bloodstream, respiratory tract, and skin and skin structure infections and included subsets R to oxacillin (OXA), vancomycin (VAN) and penicillin (PEN) to assess potential for cross-resistance.

Results: All tested GP isolates were inhibited by ≤128 µg/ml of OMI. OMI was active against *S. aureus* (SA) with MIC values ranging from 2-32 µg/ml ($MIC_{50/90}$, 16 µg/ml); and was 4-fold more active against coagulase-negative staphylococci (CNS; $MIC_{50/90}$; 4 µg/ml). OMI was 16-fold more active against *E. faecium* (EFM; $MIC_{50/90}$ results, 4/8) than *E. faecalis* (EF; 64/128 µg/ml). β-haemolytic streptococci (BHS) were slightly more S than viridans group streptococci (VGS; MIC_{90}, 32 and 128 µg/ml, respectively). OMI (MIC_{90} potency) was active across a wide range of GP (SA, CNS, EF, EFM, BHS, VGS) including OXA-, VAN- and PEN-R subsets.

	OMI MIC in µg/ml		
Organism (no. tested)	50%	90%	Range
S. aureus (110)	16	16	2-32
Coagulase-negative staphylococci (104)	4	4	1-8
Enterococcus spp. (111)	8	128	2-128
E. faecalis (44)	64	128	32-128
E. faecium (67)	4	8	2-16
ß-haemolytic streptococci (30)	16	32	16-32
Viridans group streptococci (35)	32	128	8-128

Conclusion: At a 1% (10,000 µg/ml) topical formulation, OMI can be expected to inhibit all clinically relevant GP species that produce CAI (highest documented MIC, 128 µg/ml), including OXA-, VAN- and PEN-R strains.

INTRODUCTION

Omiganan is a novel cationic peptide analog of indolicidin that is being developed as a topical antimicrobial, and is in the late stages of a Phase III clinical trial targeting prevention of catheter-related infections. The compound has a broad spectrum of cidal activity including Gram-positive and -negative bacterial species and, importantly, yeast, including emerging resistant strains. The development of most catheter-related blood stream infections are thought to arise from colonization of the catheter and infection of tissues at the site of catheter placement; the most commonly occurring organisms include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus* (including oxacillin- [methicillin]-resistant strains; MRSA), *Pseudomonas* spp., *Enterococcus* spp., Enterobacteriaceae, *Candida* spp., and *Streptococcus* spp., among others.

Given the importance of Gram-positive pathogens in producing local catheter-site and catheter-related bloodstream infections, prevention of colonization of catheters by these pathogens can be expected to have significant impact on overall patient morbidity and mortality, and related health care costs (primarily extended hospital stays and additional treatment). The purpose of this study was to update and expand the analysis of omiganan activity against prevalent Gram-positive pathogens, to better characterize the compound's breadth of spectrum and potency against recently recovered clinical isolates.

MATERIALS AND METHODS

Organism collection studied: Activity of omiganan was determined against contemporary (2005-2006 USA isolates) Gram-positive pathogens originating from bloodstream, respiratory tract or skin and skin structure infections. Organisms examined (390 isolates) included *S. aureus* (110; oxacillin-susceptible [MSSA; 49], oxacillin-resistant [MRSA; 30] and CA-MRSA, USA300 strains [31]); coagulase-negative staphylococci (104; oxacillin-susceptible [43] and oxacillin-resistant [61]); *E. faecalis* (44; vancomycin-susceptible [24] and vancomycin-resistant [20]); *E. faecium* (67; vancomycin-susceptible [31] and vancomycin-resistant [36]); ß-haemolytic-streptococci (30); and viridans group streptococci (35; penicillin-susceptible [15]; penicillin-intermediate [5]; and penicillin-resistant [15]).

Susceptibility test methods: Broth microdilution MIC testing was performed according to Clinical and Laboratory Standards Institute (CLSI) methods (documents M7-A7 [2006] and M100-S17 [2007]). Panels were produced by JMI Laboratories using either cation-adjusted Mueller-Hinton broth (with addition of 2 - 5 % lysed horse blood supplements for testing of fastidious streptococci). Interpretive criteria for comparator agents, where available, were those as published by CLSI (M100-S17; 2007).

Other breakpoints utilized (see references for discussion of breakpoints for the following agents) were: mupirocin at ≤8 µg/ml (susceptible) and high level resistance at >256 µg/ml; neomycin at ≤10 µg/ml (susceptible); bacitracin at ≤ 3.12 µg/ml (susceptible); and fusidic acid at <2 µg/ml (susceptible). The TAO breakpoint used was that of the most active component (neomycin, polymyxin B or bacitracin).

Quality control (QC) was performed per M7-A7 [2006] and M100-S17 [2007] recommendations and guidelines (omiganan QC ranges are as specified by Anderegg et al, J Clin Microbiol 2004; 42:1386-1387) using the following strains: *S. aureus* ATCC 29213, *S. pneumoniae* ATCC 49619 and *E. faecalis* ATCC 29212. All routine QC results for comparison antimicrobial agents were within the control ranges (where available) as specified.

RESULTS

- All tested Gram-positive isolates were inhibited by ≤128 µg/ml of omiganan (Table 1) with coagulase-negative staphylococci displaying the lowest MIC values (1 µg /ml) and enterococci and viridians group streptococci the highest (128 µg/ml).
- Omiganan was four-fold more active against coagulase-negative staphylococci ($MIC_{50/90}$; 4 µg/ml) than against *S. aureus* ($MIC_{50/90}$, 16 µg/ml), although all isolates were inhibited by 32 µg/ml; Table 1).
- Omiganan was also consistently more active against *E. faecium* ($MIC_{50/90}$ results, 4/8 µg/ml) than against *E. faecalis* (64/128 µg/ml; 16-fold higher; Tables 1 and 2).
- β-haemolytic streptococci were slightly more susceptible to omiganan than were viridans group streptococci (MIC_{90}, 32 and 128 µg/ml, respectively).
- Presence of commonly-occurring resistance mechanisms (oxacillin resistance in staphylococci, vancomycin resistance in enterococci, and penicillin resistance in streptococci) had no effect on MIC_{90} potency measurements of omiganan (Tables 1 and 2).
- Among tested agents, fusidic acid (MIC_{90}, 0.25 µg/ml), TAO and vancomycin also remained active against *S. aureus* and coagulase-negative staphylococci. Notably, 1.8 and 4.8%, respectively, of these species displayed MIC values to mupirocin that were >256 µg/ml (high-level resistance). Against *S. aureus*, TAO susceptibilities varied from 83.7% for MSSA to 16.7% for MRSA (data not shown).
- While a breakpoint for omiganan has not been proposed, MIC values above 1024 µg/ml have not been described (Sader et al, 2004, Antimicrob. Agents Chemother. 48:3112-8 and Table 1) and the population appears unimodal (exclusively wildtype). The clinically applied topical formulation of 10,000 µg/ml

Table 1. Cumulative percent inhibited at omiganan MIC values tested against eight groups of Gram-negative bacterial pathogens.

	Cumulative % inhibited at MIC values (µg/ml):												
Organism group (no. tested)	≤0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
S. aureus (110)	0	0	1	2	10	92	100	-	-	-	-	-	-
Oxacillin-susceptible (49)	0	0	2	4	16	96	100	-	-	-	-	-	-
Oxacillin-resistant (30)	0	0	0	0	10	87	100	-	-	-	-	-	-
Community-acquired MRSA (31)	0	0	0	0	0	90	100	-	-	-	-	-	-
Coagulase-negative staphylococci (104)	0	1	26	93	100	-	-	-	-	-	-	-	-
Oxacillin-susceptible (43)	0	2	44	98	100	-	-	-	-	-	-	-	-
Oxacillin-resistant (61)	0	0	13	90	100	-	-	-	-	-	-	-	-
Enterococcus spp.(111)	0	0	5	39	59	60	63	88	100	-	-	-	-
E. faecalis (44)	0	0	0	0	0	0	7	70	100	-	-	-	-
Vancomycin-susceptible (24)	0	0	0	0	0	0	0	54	100	-	-	-	-
Vancomycin-resistant (20)	0	0	0	0	0	0	15	90	100	-	-	-	-
E. faecium (67)	0	0	9	64	97	100	-	-	-	-	-	-	-
Vancomycin-susceptible (31)	0	0	10	48	94	100	-	-	-	-	-	-	-
Vancomycin-resistant (36)	0	0	8	78	100	-	-	-	-	-	-	-	-
ß -hemolytic streptococci (30)	0	0	0	0	0	50	100	-	-	-	-	-	-
Viridans group streptococci (35)	0	0	0	0	9	14	60	83	100	-	-	-	-
Penicillin-susceptible (15)	0	0	0	0	13	27	67	93	100	-	-	-	-
Penicillin-intermediate (5)	0	0	0	0	0	0	60	60	100	-	-	-	-
Penicillin-resistant (15)	0	0	0	0	7	7	53	80	100	-	-	-	-

a. ESBL = extended-spectrum β-lactamase producer; AmpC = AmpC enzyme hyperproducer (derepressed)

Table 2. Activity of omiganan and comparator topical antimicrobial agents tested against Gram-positive bacterial species (390 isolates).

Organism (no. tested) Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
S. aureus (110)				
Omiganan	16	16	2 - 32	- / -
Bacitracin	25	400	≤3.125 - >400	8.2 / -
Erythromycin	>8	>8	≤0.12 - >8	26.4 / 73.6
Fusidic acid	0.12	0.25	0.12 - 16	99.1 / -
Gentamicin	≤0.25	0.5	≤0.25 - >16	97.3 / 2.7
Levofloxacin	0.25	>8	≤0.06 - >8	74.5 / 25.5
Mupirocin	≤4	≤4	≤4 - >256	96.4 / 1.8
Neomycin	>16	>16	≤0.12 - >16	43.0 / -
Oxacillin	>2	>2	≤0.25 - >2	44.5 / 55.5
TAO	9.8	20	≤1.2 - 78	43.0 / -
Vancomycin	1	1	0.25 - 2	100.0 / 0.0
Coagulase-negative staphylococci (104)				
Omiganan	4	4	1 - 8	- / -
Bacitracin	25	25	≤3.125 - 400	4.8 / -
Erythromycin	>8	>8	≤0.12 - >8	33.7 / 65.4
Fusidic acid	0.12	0.25	0.06 - 16	96.1 / -
Gentamicin	≤0.25	>16	≤0.25 - >16	66.3 / 26.0
Levofloxacin	2	>8	≤0.06 - >8	47.1 / 49.0
Mupirocin	≤4	256	≤4 - >256	89.4 / 4.8
Neomycin	≤0.12	2	≤0.12 - >16	94.2 / -
Oxacillin	2	>2	≤0.25 - >2	41.3 / 58.7
TAO	≤1.2	≤1.2	≤1.2 - 20	94.2 / -
Vancomycin	2	2	0.5 - 4	100.0 / 0.0
Enterococcus faecium (67)				
Omiganan	4	8	2 - 16	- / -
Ampicillin	>8	>8	≤1 - >8	10.4 / 89.6
Bacitracin	6.25	25	≤3.125 - 50	13.4 / -
Erythromycin	>8	>8	0.25 - >8	1.5 / 92.5
Fusidic acid	4	4	0.25 - 8	6.0 / -
Gentamicin (HL)	≤500	>500	≤500 - >500	86.6 / 13.4
Levofloxacin	>8	>8	1 - >8	9.0 / 88.1
Mupirocin	≤4	8	≤4 - 8	100.0 / 0.0
Neomycin	>16	>16	2 - >16	23.9/ -
Oxacillin	>2	>2	2 - >2	- / -
TAO	9.8	78	≤1.2 - 156	23.9 / -
Vancomycin	>16	>16	0.5 - >16	46.3 / 53.7
Enterococcus faecalis (44)				
Omiganan	64	128	32 - 128	- / -
Ampicillin	≤1	≤1	≤1 - 2	100.0 / 0.0
Bacitracin	25	>400	6.25 - >400	0.0 / -
Erythromycin	>8	>8	≤0.12 - >8	11.4 / 70.5
Fusidic acid	4	4	2 - 8	0.0 / -
Gentamicin (HL)	≤500	>500	≤500 - >500	50.0 / 50.0
Levofloxacin	>8	>8	0.5 - >8	43.2 / 56.8
Mupirocin	256	256	256	0.0 / 0.0
Neomycin	>16	>16	16 - >16	0.0 / -
Oxacillin	>2	>2	0.5 - >2	- / -
TAO	78	313	9.8 - 625	0.0 / -
Vancomycin	2	>16	0.5 - >16	54.5 / 45.5
ß-haemolytic streptococci (30)				
Omiganan	16	32	16 - 32	- / -
Bacitracin	6.25	25	≤3.125 - 200	40.0 / -
Clindamycin	≤0.5	≤0.5	≤0.5 - >4	0.0 / 10.0
Erythromycin	0.06	>2	≤0.03 - >2	70.0 / 30.0
Fusidic acid	4	8	2 - 8	0.0 / -
Gentamicin	8	>16	4 - >16	- / -
Levofloxacin	0.5	1	0.25 - 1	100.0 / 0.0
Mupirocin	≤4	8	≤4 - 8	100.0 / 0.0
Neomycin	>16	>16	16 - >16	0.0 / -
Penicillin	≤0.03	≤0.03	≤0.03 - 0.06	100.0 / -
TAO	4.9	39	4.9 - 39	40.0 / -
Vancomycin	0.5	0.5	0.25 - 0.5	100.0 / -
Viridans group streptococci (35)				
Omiganan	32	128	8 - 128	- / -
Bacitracin	6.25	12.5	≤3.125 - 25	34.3 / -
Clindamycin	≤0.5	≤0.5	≤0.5 - >4	0.0 / 8.6
Erythromycin	2	>2	≤0.03 - >2	28.6 / 68.6
Fusidic acid	4	8	1 - 16	94.3 / -
Gentamicin	2	>16	0.25 - >16	- / -
Levofloxacin	0.5	8	0.12 - >8	88.6 / 11.4
Mupirocin	8	256	≤4 - >256	6.0 / 2.9
Neomycin	16	>16	0.5 - >16	28.6 / -
Penicillin	2	>4	≤0.03 - >4	42.9 / 42.9
TAO	9.8	78	≤1.2 - 156	34.3 / -
Vancomycin	0.5	0.5	0.12 - 0.5	100.0 / -

a. Susceptibility defined by the CLSI [2007], β-lactam susceptibility should be directed by the oxacillin test results. Also the following criteria: mupirocin at ≤8 µg/ml (susceptible) and high level resistance at >256 µg/ml; neomycin at ≤10 µg/ml (susceptible); bacitracin at ≤3.12 µg/ml (susceptible); and fusidic acid at <2 µg/ml (susceptible); - = no interpretive criteria. The TAO breakpoint is that of the most active component (neomycin, polymyxin B or bacitracin).

CONCLUSIONS

- In the current clinical formulation 1% gel (topical concentration, 10,000 µg/ml), omiganan is active against all the commonly isolated Gram-positive pathogens known to produce catheter-associated infections including oxacillin-, vancomycin- and penicillin-resistant strains (highest documented MIC, 128 µg/ml).
- None of the topically utilized comparator agents tested retains a spectrum that compares with that of omiganan, which when coupled with this compound's previously described activity against recognized Gram-negative bacteria and fungal pathogens, represents a 'first-in-class' agent that displays antimicrobial coverage of all major pathogens responsible for local catheter site and catheter-related bloodstream infections.
- Ongoing surveillance of antimicrobial susceptibility of Gram-positive bacterial pathogens implicated in intravascular catheter-related infections is warranted to anticipate resistance trends, and susceptibility testing for omiganan should be included.

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