E-2091

ANTIMICROBIAL ACTIVITY OF OMIGANAN PENTAHYDROCHLORIDE AGAINST CONTEMPORARY (2005-2006) GRAM-NEGATIVE PATHOGENS RESPONSIBLE FOR LOCAL CATHETER SITE INFECTIONS

PR RHOMBERG, JM STREIT, RN JONES, TR FRITSCHE

JMI Laboratories, North Liberty, IA

ICAAC 2007
JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370
fax 319.665.3371
thomas-fritsche@jmilabs.com

ABSTRACT

Background: Omiganan (OMI) is a rapidly bactericidal and fungicidal cationic peptide currently in a Phase III clinical trial for topical use in prevention of catheter-associated infections and in preclinical development for other indications. We present the spectrum and potency of OMI and comparator agents against recently collected Gram-negative pathogens.

Methods: 167 clinical isolates from USA patients with bloodstream or skin and soft tissue infections were collected (2005-2006) and susceptibility (S) tested against OMI and comparator agents using CLSI broth microdilution methods. Isolates included 43 *E. coli* (EC; 11 ESBL), 41 *Klebsiella* spp. (KSP; 11 ESBL), 42 *Enterobacter* spp. (EBS; 12 AmpC producers) and 41 *P. aeruginosa* (PSA; 10 carbapenem-resistant [CARB-R]) to monitor for cross-resistance.

Results: Rank order of OMI activity (MIC_{50}, µg/ml) was: EC (32) = KSP (32) > EBS (64) > PSA (128). Highest MIC results were found among EBS (1024 µg/ml) and KSP (512 µg/ml) isolates, well below the topical formulation concentration of 1% (10,000 µg/ml). ESBL-producing EC and KSP isolates had identical S to OMI ($MIC_{50/90}$ results, 32/32 and 256/256 µg/ml, respectively) compared to wild type (WT) strains. AmpC-producing EBS showed lower OMI $MIC_{50/90}$ results (32/64 µg/ml) than WT strains (64/512 µg/ml). CARB-S and CARB-R PSA strains were equally S to OMI ($MIC_{50/90}$ results identical, 128/256).

Organism (no. tested)	Omiganan MIC in µg/ml 50%	90%	Range
E. coli (43)	32	32	8-64
Klebsiella spp. (41)	32	256	8-512
Enterobacter spp. (42)	64	512	8-1024
Pseudomonas aeruginosa (41)	128	256	32-256
All Enterobacteriaceae (126)	32	256	8-1024
All Gram-negative bacilli (167)	64	256	8-1024

Conclusion: At the clinical formulation concentration of 1% (10,000 µg/ml) OMI can be expected to inhibit skin colonization by GN pathogens known to produce catheter-associated infections, including those with problematic R mechanisms, with no evidence of cross-resistance.

INTRODUCTION

Omiganan is a novel cationic peptide analog of indolicidin that has a broad spectrum of cidal activity including Gram-positive and -negative bacterial species and, importantly, yeast. This agent is being developed as a topical antimicrobial, and is currently in a Phase III clinical trial targeting the prevention of local catheter-site infections and, secondarily, catheter-related bloodstream infections. 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. Various studies have identified the most commonly occurring pathogens that include coagulase-negative staphylococci (CoNS), *Staphylococcus aureus*, *Pseudomonas* spp., Enterobacteriaceae, *Candida* spp., and *Enterococcus* spp., among others.

Given the importance of Gram-negative bacilli second to Gram-positive cocci as the most prevalent pathogens producing local catheter-site and catheter-related bloodstream infections, prevention of their occurrence 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 continued emergence of resistance among Gram-negative infections further confounds this problem and poses special challenges in patient management.

The purpose of this study was to update and expand the analysis of omiganan activity against prevalent Gram-negative 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-origin isolates) Gram-negative pathogens recovered from patients with bloodstream or skin and skin structure infections. Organisms examined (167 isolates) included: *E. coli* (43; wildtype [32] and ESBL-producers [11]); *Klebsiella* spp. (41; wildtype [30] and ESBL-producers [11]; *Enterobacter* spp. (42; wildtype [30] and derepressed AmpC mutants [12]); and *P. aeruginosa* (41; carbapenem-susceptible [30], carbapenem-intermediate [1] and carbapenem-resistant [10]).

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 cation-adjusted Mueller-Hinton broth. Interpretive criteria for most comparator agents were those as published by CLSI (M100-S17; 2007). The breakpoint utilized for neomycin was ≤10 µg/ml (susceptible; see references for discussion). 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 using the following strains: *E. coli* ATCC 25922 and *P. aeruginosa* ATCC 27853. Omiganan QC ranges are as specified by Anderegg et al (J Clin Microbiol 2004; 42: 1386-1387). All routine QC results for comparison antimicrobial agents were within the control ranges (where available) as specified by CLSI M100-S17.

RESULTS

- Rank order of omiganan activity (MIC_{50}, µg/ml) against Gram-negative pathogens was: *E. coli* = *Klebsiella* spp. (32) > *Enterobacter* spp. (64) > *P. aeruginosa* (128; Table 1).
- Highest MIC results were found among *Enterobacter* spp. (up to 1024 µg/ml) and *Klebsiella* spp. (512 µg/ml) isolates, well below the topical formulation concentration of 1% (10,000 µg/ml; Tables 1 and 2).
- Extended-spectrum β-lactamase (ESBL)-producing *E. coli* and *Klebsiella* spp. isolates had identical susceptibility profiles to omiganan ($MIC_{50/90}$ results, 32/32 and 256/256 µg/ml, respectively) compared to wild-type strains (Table 1).
- Derepressed AmpC-producing *Enterobacter* spp. showed lower omiganan $MIC_{50/90}$ results (32/64 µg/ml) than wildtype strains (64/512 µg/ml; Table 1).
- Carbapenem-susceptible and -resistant *P. aeruginosa* strains were equally susceptible to omiganan ($MIC_{50/90}$, 128/256; Table 1).
- While TAO and its active components neomycin and polymyxin-B inhibited *E. coli* (100%), *Klebsiella* spp. (97.6%) and *P. aeruginosa* (100%; Table 1), they were less active against ESBL-positive *Klebsiella* spp. (90.9%), unlike omiganan (data not shown).
- While a breakpoint for omiganan has not been proposed, MIC values above 1024 µg/ml have not been described here or elsewhere, and the population appears unimodal (exclusively wildtype). The clinically applied topical formulation of 10,000 µg/ml is almost 10-fold greater than the highest recorded omiganan MIC value.

Table 2 Activity of omiganan and comparator antimicrobial agents tested against Gram-negative pathogens (167 isolates).

Organism (no. tested)/ Antimicrobial agent	MIC_{50}	MIC_{90}	Range	% susceptible/resistant[a]
Enterobacteriaceae (126)				
Omiganan	32	256	8 - 1024	- / -
Ceftazidime	0.5	>16	≤0.12 - >16	74.6 / 23.8
Ceftriaxone	≤0.25	>32	≤0.25 - >32	77.8 / 17.5
Ciprofloxacin	0.015	>8	≤0.004 - >8	81.0 / 18.3
Gentamicin	0.5	16	≤0.12 - 256	88.1 / 10.3
Imipenem	0.12	0.5	≤0.015 - 2	100.0 / 0.0
Neomycin	1	2	0.25 - 32	92.9 / -
Polymyxin B	0.25	0.5	0.12 - >8	93.7 / 6.3
TAO	≤1.2	≤1.2	≤1.2 - 4.9	93.7/ -
E. coli (43)				
Omiganan	32	32	8 - 64	- / -
Ceftazidime	0.5	>16	≤0.12 - >16	76.7 / 23.3
Ceftriaxone	≤0.25	>32	≤0.25 - >32	79.1 / 20.9
Ciprofloxacin	0.015	>8	≤0.004 - >8	69.8 / 30.2
Gentamicin	0.5	2	0.25 - 128	90.7 / 9.3
Imipenem	0.12	0.25	0.06 - 0.25	100.0 / 0.0
Neomycin	1	4	0.5 - 32	95.3 / -
Polymyxin B	0.25	0.5	0.12 - 0.5	100.0 / 0.0
TAO	≤1.2	≤1.2	≤1.2 - 4.9	100.0 / -
Klebsiella spp. (41)				
Omiganan	32	256	8 - 512	- / -
Ceftazidime	0.5	>16	≤0.12 - >16	75.6 / 22.0
Ceftriaxone	≤0.25	32	≤0.25 - >32	80.5 / 7.3
Ciprofloxacin	0.015	>8	≤0.004 - >8	80.5 / 17.1
Gentamicin	0.25	8	≤0.12 - 128	85.4 / 9.8
Imipenem	0.12	0.25	≤0.015 - 0.5	100.0 / 0.0
Neomycin	0.5	16	0.5 - 32	85.4 / -
Polymyxin B	0.25	0.5	0.12 - 8	97.6 / 2.4
TAO	≤1.2	≤1.2	≤1.2 - 4.9	97.6 / -
Enterobacter spp. (42)				
Omiganan	64	512	8 - 1024	- / -
Ceftazidime	0.5	>16	0.25 - >16	71.4 / 26.2
Ceftriaxone	≤0.25	>32	≤0.25 - >32	73.8 / 23.8
Ciprofloxacin	0.015	0.5	0.008 - >8	92.9 / 7.1
Gentamicin	0.25	64	0.25 - 256	88.1 / 11.9
Imipenem	0.25	1	0.12 - 2	100.0 / 0.0
Neomycin	0.5	1	0.25 - 16	97.6 / -
Polymyxin B	0.25	>8	0.12 - >8	83.3 / 16.7
TAO	≤1.2	≤1.2	≤1.2	97.6 / -
P. aeruginosa (41)				
Omiganan	128	256	32 - 256	- / -
Ceftazidime	4	>16	2 - >16	80.5 / 14.6
Ceftriaxone	32	>32	8 - >32	4.9 / 26.8
Ciprofloxacin	0.12	>8	0.06 - >8	78.0 / 14.6
Gentamicin	2	8	0.25 - >256	80.5 / 7.3
Imipenem	1	16	0.5 - >16	73.2 / 24.4
Neomycin	8	128	2 - >256	65.8 / -
Polymyxin B	0.5	0.5	0.25 - 1	100.0 / 0.0
TAO	≤1.2	≤1.2	≤1.2	100.0 / -

a. Susceptibility defined by the CLSI [2007] and the following criteria: neomycin at ≤10 µg/ml (susceptible only); polymyxin B at ≤2 µg/ml (susceptible) and ≤4 µg/ml (resistant); - = no interpretive criteria. The TAO breakpoint is that of the most active component (neomycin or polymyxin B).

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

Organism group (no. tested)	Cumulative % inhibited at MIC values (µg/ml): ≤0.5	1	2	4	8	16	32	64	128	256	512	1024	>1024
Escherichia coli (43)	0	0	0	0	9	14	98	100	-	-	-	-	-
Wild-type (32)	0	0	0	0	6	13	97	100	-	-	-	-	-
ESBL[a] (11)	0	0	0	0	18	18	100	-	-	-	-	-	-
Klebsiella spp. (41)	0	0	0	0	22	27	51	54	63	90	100	-	-
Wild-type (30)	0	0	0	0	20	27	57	60	63	90	100	-	-
ESBL[a] (11)	0	0	0	0	27	27	36	36	64	91	100	-	-
Enterobacter spp. (42)	0	0	0	0	10	10	43	76	79	88	95	100	-
Wild-type (30)	0	0	0	0	10	10	33	67	70	83	93	100	-
AmpC[a] (12)	0	0	0	0	8	8	67	100	-	-	-	-	-
P. aeruginosa (41)	0	0	0	0	0	0	2	10	68	100	-	-	-
Carbapenem-susceptible (30)	0	0	0	0	0	0	0	10	70	100	-	-	-
Carbapenem-resistant (10)	0	0	0	0	0	0	10	10	60	100	-	-	-

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

CONCLUSIONS

- In the current clinical formulation 1% gel (topical concentration, 10,000 µg/ml), omiganan is active against the commonly isolated Gram-negative pathogens known to produce catheter-associated infections and reported here (highest documented MIC, 1024 µg/ml), including strains resistant to advanced generation cephalosporins (ESBL-producers) and to carbapenems (*P. aeruginosa*) with no evidence of cross-resistance.
- 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-positive 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-negative bacterial pathogens implicated in intravascular catheter related infections is warranted to anticipate resistance trends, and susceptibility testing for omiganan should be included.

SELECTED REFERENCES

Anderegg TR, Fritsche TR, Jones RN (2004). Quality control guidelines for MIC susceptibility testing of omiganan pentahydrochloride (MBI 226), a novel antimicrobial peptide. *J Clin Microbiol* 42: 1386-1387.

Clinical and Laboratory Standards Institute. (2006). *M7-A7, Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; approved standard - seventh edition*. Wayne, PA: CLSI.

Clinical and Laboratory Standards Institute. (2007). *M100-S17, Performance standards for antimicrobial susceptibility testing, 17th informational supplement*. Wayne, PA: CLSI.

Jones RN, Li Q, Kohut B, Biedenbach DJ, Bell J, Turnidge JD (2006). Contemporary antimicrobial activity of triple antibiotic ointment: a multiphased study of recent clinical isolates in the United States and Australia. *Diagn Microbiol Infect Dis* 54: 63-71.

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.

Sader HS, Fedler KA, Rennie RP, Stevens S, Jones RN (2004). Omiganan pentahydrochloride (MBI 226), a topical 12-amino-acid cationic peptide: Spectrum of antimicrobial activity and measurements of bactericidal activity. *Antimicrob Agents Chemother* 48: 3112-3118.

Viale P, Stefani S (2006). Vascular catheter-associated infections: A microbiological and therapeutic update. *J Chemother* 18: 235-249.