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ACTIVITY OF OMIGANAN PENTAHYDROCHLORIDE AGAINST YEAST AND MOULD PATHOGENS ASSOCIATED WITH CATHETER COLONIZATION AND CATHETER-RELATED BLOODSTREAM INFECTIONS

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ABSTRACT

Background: Omiganan (OMI) is a rapidly bactericidal and fungicidal cationic peptide that is known to significantly reduce normal skin flora following topical applications. OMI is currently in a Phase III USA and European clinical trial for 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 common yeast and mould species.

Methods: 126 fungal isolates (*Candida* spp. [CSP], 106; moulds, 20; see Table) were collected from USA patients and were susceptibility (S) tested against OMI and comparator agents by CLSI broth microdilution methods. All endpoints were read at 48-hours as recommended. Isolates originated from sterile site infections (bloodstream, respiratory tract or deep tissues).

Results: OMI inhibited all CSP isolates at ≤256 µg/ml, being most active against *C. albicans*, *C. krusei* and *C. tropicalis* (MIC_{50} values, 32-64 µg/ml; see Table). All CSP isolates were inhibited within a four dilution range of OMI (16 to 256 µg/ml). OMI displayed similar antifungal activity (MIC_{50}, 64 µg/ml) against CSP with intrinsic resistance to fluconazole (FLU; *C. krusei*, MIC_{50}, 32 µg/ml) compared with *C. albicans* (FLU MIC_{50}, 1 µg/ml). Moulds, including *Aspergillus* spp., displayed 2-fold higher OMI MIC results (up to 1024 µg/ml) than did yeast, but all MIC values were well below the topical formulation concentration of 1% (10,000 µg/ml).

	Omiganan MIC in µg/ml		
Organism (no.)	50%	90%	Range
All yeast (106)	64	256	16-256
C. albicans (52)	64	128	32-128
C. glabrata (22)	256	256	128-256
C. krusei (10)	64	128	32-128
C. parapsilosis (11)	128	256	32-256
C. tropicalis (11)	32	32	16-32
Moulds (20)	128	1024	1-1024
Aspergillus spp. (10)	64	1024	16-1024

Conclusion: OMI inhibited all tested CSP and mould isolates at concentrations well below that of the 1% (10,000 µg/ml) topical formulation, including species with reduced susceptibility to azoles and echinocandins.

INTRODUCTION

Omiganan is a rapidly bactericidal and fungicidal cationic peptide analog of indolicidin that is known to significantly reduce normal skin flora counts following topical applications. This agent is being developed as a topical antimicrobic and is currently in a Phase III USA and European clinical trial for prevention of catheter-associated infections and in preclinical development for other indications.

Prevention of local catheter site infections by both bacterial and fungal pathogens is an important component in controlling nosocomial bloodstream infections and improving patient outcomes. While staphylococci and enterococci produce most catheter-associated infections, data from the National Nosocomial Infections Surveillance (NNIS) system has shown that approximately 8% are produced by *Candida* spp. Given the importance of fungi as pathogens in compromised hosts and difficulty in medical management of these 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 emergence of resistance among fungal pathogens, either appearing de novo or through selection of species with intrinsic resistance mechanisms 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 fungal 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 fungal pathogens (2005-2006, or earlier for more rare species) responsible for catheter colonization and catheter-related bloodstream infections. All organisms originated from sterile site infections (126 isolates; bloodstream, respiratory tract and deep tissues) and included: *C. albicans* (52), *C. glabrata* (22), *C. tropicalis* (11), *C. parapsilosis* (11), *C. krusei* (10), *Aspergillus* spp. (10) and other mould species (10).

Susceptibility test methods: Broth microdilution MIC testing was performed according to Clinical and Laboratory Standards Institute (CLSI) methods (M27-A2; 2002). Panels were produced by JMI Laboratories using RPMI 1640 broth supplemented with MOPS (morpholinepropane-sulfonic acid) buffer. All results were recorded at 48 hours as specified and interpretive criteria for comparator agents were those as published in CLSI M27-S2 (2006). Quality control (QC) was performed as recommended in M27-A2 (2002) using the following QC strains: *C. parapsilosis* ATCC 22019 and *C. krusei* ATCC 6258. Omiganan QC ranges for these organisms are as specified by Anderegg et al, J Clin Microbiol 2004; 42:1386-1387. All routine QC results for omiganan and comparator antifungal agents were within the specified control ranges.

RESULTS

- Omiganan inhibited all *Candida* spp. isolates within a five $\log_2$ dilution range (16 to 256 µg/ml), being most active against *C. tropicalis*, *C. albicans* and *C. krusei* ($MIC_{50/90}$ values, 32/32-64 µg/ml) and least active against *C. glabrata* and *C. parapsilosis* ($MIC_{50/90}$ values, 128-256/256 µg/ml; Table 1).
- Omiganan displayed similar antifungal activity (MIC_{50}, 64 µg/ml) against *Candida* species with intrinsic resistance to azole agents (*C. krusei*; fluconazole MIC_{50}, 32 µg/ml) compared with that of *C. albicans* (MIC_{50}, 1 µg/ml; Table 2).
- Moulds, including *Aspergillus* spp., displayed two-fold higher omiganan MIC results (up to 1024 µg/ml; Tables 1 and 2) than did yeast, but all MIC values were well below the topical formulation concentration of 1% (10,000 µg/ml).
- Among comparator antifungal agents, results were highly variable and species-dependent, with *C. krusei* being largely resistant to all agents except voriconazole (Table 2). Only amphotericin B and omiganan (MIC_{90} values, 1-2 and 32-256 µg/ml, respectively) displayed consistent activity against all yeast and mould species.

Table 1. Cumulative percent inhibited at omiganan MIC values tested against six groups of yeasts and moulds (126

	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
Candida spp. (106)	0	0	0	0	0	4	14	51	81	100	-	-	-
C. albicans (52)	0	0	0	0	0	0	2	65	100	-	-	-	-
C. glabrata (22)	0	0	0	0	0	0	0	0	18	100	-	-	-
C. krusei (10)	0	0	0	0	0	0	20	70	100	-	-	-	-
C. parapsilosis (11)	0	0	0	0	0	0	9	18	82	100	-	-	-
C. tropicalis (11)	0	0	0	0	0	36	100	-	-	-	-	-	-
Moulds (20)	0	5	5	5	15	20	25	45	60	80	80	100	-

Table 2. Activity of omiganan and comparator antifungal agents tested against yeast and mould pathogens (126

Organism (no.tested)/ Antimicrobial Agent	MIC_{50}	MIC_{90}	Range	% Susceptible/ Resistant[a]
Candida albicans (52)				
Omiganan	64	128	32 - 128	- / -
Amphotericin B	1	1	0.5 - 1	- / -
Fluconazole	1	>64	0.12 - >64	67.3 / 30.8
5-Flucytosine	0.12	1	≤0.03 - 2	100.0 / 0.0
Itrazconazole	0.12	16	≤0.008 - 16	50.0 / 48.1
Nystatin	8	8	8	- / -
Voriconazole	0.03	>16	≤0.008 - 16	75.0 / 25.0
Candida glabrata (22)				
Omiganan	256	256	128 - 256	- / -
Amphotericin B	1	1	0.5 - 1	- / -
Fluconazole	4	>64	1 - >64	77.3 / 18.2
5-Flucytosine	0.06	0.06	≤0.03 - 0.06	100.0 / 0.0
Itrazconazole	0.12	0.5	0.03 - 1	72.7 / 4.6
Nystatin	8	8	8	- / -
Voriconazole	0.06	2	0.03 - 2	86.4 / 0.0
Candida krusei (10)				
Omiganan	64	128	32 - 128	- / -
Amphotericin B	1	2	0.5 - 2	- / -
Fluconazole	32	64	32 - 64	0.0 / 100.0
5-Flucytosine	16	32	8 - 32	0.0 / 30.0
Itrazconazole	0.5	0.5	0.12 - 0.5	10.0 / 0.0
Nystatin	8	8	8	- / -
Voriconazole	0.25	0.5	0.12 - 0.5	100.0 / 0.0
Candida parapsilosis (11)				
Omiganan	128	256	32 - 256	- / -
Amphotericin B	1	1	1	- / -
Fluconazole	0.5	16	0.5 - 16	81.8 / 0.0
5-Flucytosine	0.12	0.12	0.06 - 0.12	100.0 / 0.0
Itrazconazole	0.06	0.25	0.015 - 0.25	63.6 / 0.0
Nystatin	8	8	8	- / -
Voriconazole	0.015	0.12	≤0.008 - 0.12	100.0 / 0.0
Candida tropicalis (11)				
Omiganan	32	32	16 - 32	- / -
Amphotericin B	1	1	0.5 - 1	- / -
Fluconazole	0.25	>64	0.12 - >64	81.8 / 18.2
5-Flucytosine	0.06	0.12	0.06 - 0.12	100.0 / 0.0
Itrazconazole	0.03	0.12	0.015 - 0.12	100.0 / 0.0
Nystatin	8	8	8	- / -
Voriconazole	0.015	16	0.015 - 16	72.7 / 27.3
Moulds (20; including 10 *Aspergillus* spp.)				
Omiganan	128	1024	1 - 1024	- / -
Amphotericin B	0.5	1	0.015 - 1	- / -
Fluconazole	>64	>64	1 - >64	- / -
5-Flucytosine	>64	>64	0.125 - >64	- / -
Itrazconazole	0.03	0.12	≤0.008 - 16	- / -
Nystatin	8	16	0.5 - 32	- / -
Voriconazole	0.25	2	≤0.008 - 16	- / -

a. Criteria as published by the CLSI [2006]; - = no breakpoint available.

CONCLUSIONS

- In the current clinical formulation 1% gel (topical concentration, 10,000 µg/ml), omiganan is active against all the commonly isolated fungal pathogens (highest documented MIC values, 256 and 1024 µg/ml, respectively) known to produce catheter-associated infections, including yeasts and moulds with intrinsically reduced susceptibility to azoles and echinocandins.
- Omiganan represents a 'first-in-class' topical agent that displays broad antifungal and antibacterial coverage of all major pathogens responsible for local catheter site and catheter-related bloodstream infections; none of the currently marketed topical agents retains a spectrum that is comparable.
- Ongoing surveillance of antimicrobial susceptibility of fungal pathogens implicated in intravascular catheter related infections is warranted to anticipate resistance trends, and susceptibility testing for omiganan should be included.

SELECTED REFERENCES

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