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Activity of Oritavancin against Recent Clinical Isolates of Methicillin-Resistant Staphylococci from Western Europe

Contact info:
Ian Morrissey.
Quotient Bioresearch Ltd.
Newmarket Road
Fordham
Cambs CB7 5WW
UK
Tel: +44(0)1638 722960
Email:
i.morrissey@quotientbioresearch.com

Morrissey, I.[1], H. Seifert[2], R. Canton[3], P. Nordmann[4], S. Stefani[5], A. MacGowan[6], R. Janes[1] and D. Knight[1].

[1]Quotient Bioresearch Ltd, Fordham. UK .[2]University of Koln, Koln, Germany. [3]University Ramón y Cajal, Madrid, Spain.
[4]Hopital de Bicetre, Paris, France. [5]University of Catania, Catania, Italy. [6]Southmead Hospital, Bristol, UK.

Abstract

Background: The *in vitro* activity of oritavancin (ORI) and comparators was determined against methicillin-resistant (MR) staphylococci collected in 2011 from 41 hospitals in France (FRA), Germany (GER), Italy (ITL), Spain (SPN) and the United Kingdom (UK).

Methods: 204 MR *S. aureus* (MRSA) and 177 MR coagulase-negative staphylococci (MRCNS) - mainly *S. epidermidis* (132, 75%) were submitted to a central reference laboratory and their identification was confirmed by MALDI-ToF mass spectrometry. Of these 38% of MRSA and 67% of MRCNS were from bacteraemia and the remainder from acute bacterial skin and skin structure infections. MIC was determined by CLSI broth microdilution for ORI, vancomycin (VAN), teicoplanin (TEI), daptomycin (DAP), linezolid (LZD), tigecycline (TGC), tetracycline (TET), ampicillin (AMP), clindamycin (CLI), levofloxacin (LEV) and trimethoprim-sulphamethoxazole (SXT). Susceptibility to chloramphenicol (CHL), erythromycin (ERY), kanamycin (KAN), tobramycin (TOB) and gentamicin (GEN) was determined by CLSI disk diffusion methodology. CLSI breakpoints were used throughout where available, except for TGC (EUCAST).

Results: Summary data for all isolates are given below. Susceptibility (%S) for VAN against MRSA and MRCNS was 100% in all countries. Some non-susceptibility was observed for DAP against MRSA (3 GER & 1 ITL) and MRCNS (3 GER & 1 ITL), for TGC against MRSA (1 GER) and MRCNS (5 GER & 1 ITL) and for LZD against MRCNS (3 GER). The LZD non-susceptible (NS) MRCNS had an MIC of ≥8 mg/L. Overall the MRCNS were more resistant than MRSA. By MIC50/90, ORI was at least 16-fold more potent than VAN, DAP, and LZD against MRSA and at least 8-fold more potent than these agents against MRCNS.

Conclusion: ORI showed potent activity against all MR staphylococci collected from FRA, GER, ITL, SPN and the UK during the 2011 year. Although not high, there was some evidence of resistance to newer agents such as TGC, DAP or LZD. Interestingly these were restricted to GER and/or ITL only.

Introduction

Oritavancin is a semisynthetic lipoglycopeptide currently under clinical evaluation for the treatment of acute bacterial skin and skin structure infections (ABSSSI) in adult patients. A single 1200 mg dose of oritavancin is currently being evaluated as a treatment for Gram-positive ABSSSI based on recent Phase 2 data.[1]
This current study evaluated the *in vitro* activity of oritavancin against selected, recent clinical isolates of methicillin-resistant *Staphylococcus* spp. collected from Western Europe.

Methods

Methicillin-resistant *Staphylococcus* spp. from ABSSSI or bacteraemia were sought from 41 collecting centres in Spain (8), Italy (9), Germany (8), France (8) and the United Kingdom (8) between the 1st January 2011 and 30th June 2011. Duplicate or repeat isolates from the same infection episode and methicillin-resistant coagulase-negative staphylococci cultured from less than two blood samples/patient (i.e., without confirmatory culture from blood drawn from an independent venipuncture site) were not included in the study. Isolates were re-identified at a central laboratory (Quotient Bioresearch) by Matrix Assisted Laser Desorption Ionisation Time-of-Flight Mass Spectrometry (MALDI-TOF MS). Methicillin-resistance was confirmed by measuring zone diameter of a 30 µg cefoxitin disk (≤21 mm for *S. aureus* & ≤24 mm for coagulase-negative Staphylococci), as recommended by CLSI.[2]

MIC for Oritavancin (ORI), Vancomycin (VAN), Teicoplanin (TEI), Daptomycin (DAP), Linezolid (LZD), Tigecycline (TGC), Tetracycline (TET), Ampicillin (AMP), Clindamycin (CLI), Levofloxacin (LEV) and Trimethoprim-sulphamethoxazole (SXT) was determined by broth microdilution using dried panels (Thermo Fisher, East Grinstead, UK) according to CLSI methodology.[3] In addition, susceptibility was measured by disk diffusion for Erythromycin (ERY), Chloramphenicol (CHL), Kanamycin (KAN), Tobramycin (TOB) and Gentamicin (GEN) according to CLSI methodology.[3] Susceptibility was determined using breakpoints set by CLSI.[2] Where no CLSI breakpoints exists for particular antimicrobial / bacterial isolate combinations susceptibility was determined by EUCAST breakpoints.[4] A summary of the breakpoints used are shown in Table 1. Susceptibility breakpoints for ORI have yet to be defined.

Table 1: MIC breakpoints used in this study.

Antibiotic	Susceptible breakpoint	Resistant breakpoint
AMP	≤0.25	≥0.5
CLI	≤0.5	≥4
DAP	≤1	-
LEV	≤1	≥4
LZD	≤4	≥8
SXT	≤2	≥4
TEI	≤8	≥32
TET	≤4	≥16
TGC	≤0.5	≥1
VAN	≤4 (≤2)*	≥32 (≥16)

*Data in parentheses are for coagulase-negative staphylococci.

Results – 1

A total of 381 eligible staphylococci were collected (Table 2). Summary susceptibility & MIC data by country are given Tables 3, 4 & 5.

Oritavancin was the most active antibacterial tested with MIC_{90} of 0.06 mg/L against methicillin-resistant *S. aureus* from each country and 0.12/0.25 against methicillin-resistant coagulase-negative staphylococci. A comparison between oritavancin MIC distribution and other anti-Gram-positive agents is shown in Figure 1. A few staphylococci were non-susceptible to DAP, TGC or LZD, mainly from various sites within Germany or Italy (Table 6) but remained susceptible to the other two. ORI demonstrated potent activity against all tested strains. Of the 3 LZD-resistant isolates, one may be *cfr* due to cross-resistance to CLI (Table 6) and susceptibility to ERY (data not shown).

Generally coagulase-negative staphylococci were less susceptible to the tested antibacterial agents than *S. aureus.*

Results – 2

Table 2: Geographic source of methicillin-resistant staphylococci tested in this study.

Methicillin-resistant isolates	Country					All
	France	Germany	Italy	Spain	UK	
S. aureus	37	43	41	45	38	204
S. epidermidis	24	35	27	25	21	132
S. haemolyticus	6	1	4	6	4	21
S. hominis	3		7	3	3	16
S. capitis	1	2				3
S. pettenkoferi			1		1	2
S. warneri			2			2
S. cohnii					1	1
Total	71	81	82	79	68	381

Table 3: Summary susceptibility and MIC data for oritavancin and comparators against methicillin-resistant *Staphylococcus aureus*.

		ORI	VAN	TEI	DAP	LZD	TGC	TET	AMP	CLI	LEV	SXT
All (204)	% Susceptible	-	100	100	98.5	100	99.5	87.7	1.5	70.1	9.8	99
	MIC50/90 (mg/L)	0.03/0.06	1/1	0.5/0.5	0.5/1	2/2	0.12/0.25	0.5/16	16/≥32	0.12/≥32	≥16/≥16	≤0.12/0.25
France (37)	% Susceptible	-	100	100	100	100	100	83.8	0	81.1	18.9	100
	MIC50/90 (mg/L)	0.03/0.06	1/1	0.5/0.5	0.5/0.5	2/2	0.06/0.25	0.5/8	8/≥32	0.12/≥32	8/≥16	≤0.12/≤0.12
Germany (43)	% Susceptible	-	100	100	100	100	97.7	95.3	0	25.6	2.3	100
	MIC50/90 (mg/L)	0.03/0.06	1/1	0.5/0.5	0.5/1	2/2	0.12/0.25	0.5/0.5	16/≥32	≥32/≥32	≥16/≥16	≤0.12/≤0.12
Italy (41)	% Susceptible	-	100	100	92.7	100	100	85.4	7.3	75.6	7.3	97.6
	MIC50/90 (mg/L)	0.03/0.06	1/2	0.5/2	0.5/1	2/2	0.12/0.25	0.5/≥64	16/≥32	0.12/≥32	≥16/≥16	≤0.12/0.25
Spain (45)	% Susceptible	-	100	100	100	100	100	97.8	0	84.4	8.9	100
	MIC50/90 (mg/L)	0.03/0.06	1/1	0.5/0.5	1/1	2/2	0.12/0.25	0.5/1	≥32/≥32	0.12/≥32	8/≥16	≤0.12/≤0.12
UK (38)	% Susceptible	-	100	100	100	100	100	73.7	0	86.8	13.2	97.4
	MIC50/90 (mg/L)	0.015/0.06	0.5/1	≤0.25/0.5	0.5/1	2/2	0.06/0.25	0.25/16	16/≥32	0.12/≥32	8/≥16	≤0.12/0.25

Results – 3

Table 4: Summary susceptibility and MIC data for oritavancin and comparators against methicillin-resistant Coagulase-negative staphylococci.

		ORI	VAN	TEI	DAP	LZD	TGC	TET	AMP	CLI	LEV	SXT
All (177)	% Susceptible	-	100	92.7	97.7	98.3	96.6	76.3	0.6	55.4	17.5	43.5
	MIC50/90 (mg/L)	0.06/0.12	2/4	4/8	1/1	1/2	0.25/0.5	2/≥64	8/≥32	0.25/≥32	8/≥16	4/≥8
France (34)	% Susceptible	-	100	97.1	100	100	100	76.5	0	67.6	23.5	41.2
	MIC50/90 (mg/L)	0.06/0.12	2/2	4/8	1/1	1/2	0.12/0.5	1/≥64	8/≥32	0.25/≥32	4/≥16	4/≥8
Germany (38)	% Susceptible	-	100	89.5	92.1	100	86.8	89.5	0	23.7	7.9	36.8
	MIC50/90 (mg/L)	0.06/0.25	2/4	8/16	1/1	1/2	0.25/1	2/≥64	16/16	≥32/≥32	≥16/≥16	4/≥8
Italy (41)	% Susceptible	-	100	87.8	97.6	95.1	97.6	70.7	0	68.3	19.5	53.7
	MIC50/90 (mg/L)	0.06/0.12	2/4	4/16	1/1	1/2	0.12/0.25	4/≥64	8/≥32	0.12/≥32	8/≥16	2/≥8
Spain (34)	% Susceptible	-	100	94.1	100	97.1	100	79.4	0	58.8	11.8	52.9
	MIC50/90 (mg/L)	0.06/0.12	2/4	8/8	0.5/1	1/2	0.25/0.25	1/≥64	8/≥32	0.12/≥32	8/≥16	0.5/4
UK (30)	% Susceptible	-	100	96.7	100	100	100	63.3	3.3	60	26.7	30
	MIC50/90 (mg/L)	0.06/0.12	2/4	4/8	0.5/1	1/1	0.12/0.5	4/≥64	8/≥32	0.12/≥32	4/≥16	4/≥8

Table 5: Susceptibility data for comparators tested by disk diffusion.

	Methicillin-resistant coagulase-negative Staphylococci						Methicillin-resistant *S. aureus*					
% Susceptible	All (177)	France (34)	Germany (38)	Italy (41)	Spain (34)	UK (30)	All (204)	France (37)	Germany (43)	Italy (41)	Spain (45)	UK (38)
ERY	14.7	32.4	7.9	9.8	20.6	3.3	36.3	70.3	20.9	24.4	51.1	15.8
CHL	80.8	97.1	76.3	56.1	94.1	86.7	97.1	100	100	90.2	97.8	97.4
KAN	21.5	26.5	13.2	14.6	38.2	16.7	36.8	51.4	39.5	36.6	17.8	42.1
TOB	29.9	38.2	21.1	17.1	44.1	33.3	41.2	56.8	44.2	39	26.7	42.1
GEN	30.5	44.1	18.4	19.5	44.1	30	84.3	97.3	95.3	58.5	84.4	86.8

Results – 4

Table 6: Patient/isolate details for staphylococci non-susceptible to daptomycin (N=7), linezolid (N=3) or tigecycline (N=3).

					MIC (mg/L)*				
Pathogen	Site	Age group	Gender	Infection	ORI	DAP	LZD	TGC	CLI
S. epidermidis	Germany (A)	> 65 yrs	Male	Bacteraemia	0.12	1	2	**>2**	**>16**
S. epidermidis		> 65 yrs	Male	Bacteraemia	0.25	1	2	**1**	**>16**
S. epidermidis		18 to 65 yrs	Female	Bacteraemia	0.12	**2**	1	0.5	**>16**
S. epidermidis	Germany (B)	> 65 yrs	Female	Bacteraemia	0.06	**2**	2	0.12	**>16**
S. epidermidis	Germany (C)	18 to 65 yrs	Female	Bacteraemia	0.12	1	1	**1**	0.5
S. epidermidis	Germany (D)	18 to 65 yrs	Male	Bacteraemia	0.12	0.5	2	**1**	**>16**
S. capitis	Germany (E)	18 to 65 yrs	Female	Bacteraemia	0.008	**2**	1	0.06	**>16**
S. epidermidis		> 65 yrs	Male	ABSSSI	0.12	1	1	**1**	**>16**
S. epidermidis	Italy (A)	< 5 yrs	Male	ABSSSI	0.12	1	2	**1**	**>16**
S. epidermidis	Italy (B)	18 to 65 yrs	Female	Bacteraemia	0.06	1	**>8**	0.5	**1**
S. epidermidis	Italy (C)	> 65 yrs	Female	Bacteraemia	0.06	1	**>8**	0.25	**>16**
S. pettenkoferi	Italy (D)	> 65 yrs	Male	Bacteraemia	0.008	**2**	1	0.12	0.25
S. epidermidis	Spain	> 65 yrs	Male	Bacteraemia	0.06	0.5	**>8**	0.25	**>16**
S. aureus	Germany (E)	> 65 yrs	Male	ABSSSI	0.03	1	2	**1**	**>16**
S. aureus	Italy (E)	> 65 yrs	Male	Bacteraemia	0.03	**4**	2	0.25	**1**
S. aureus		18 to 65 yrs	Male	ABSSSI	0.03	**4**	1	0.25	0.12
S. aureus	Italy (C)	18 to 65 yrs	Male	Bact	0.03	**2**	2	0.06	**>16**

***Non-susceptibility is indicated in bold.**

Results – 5

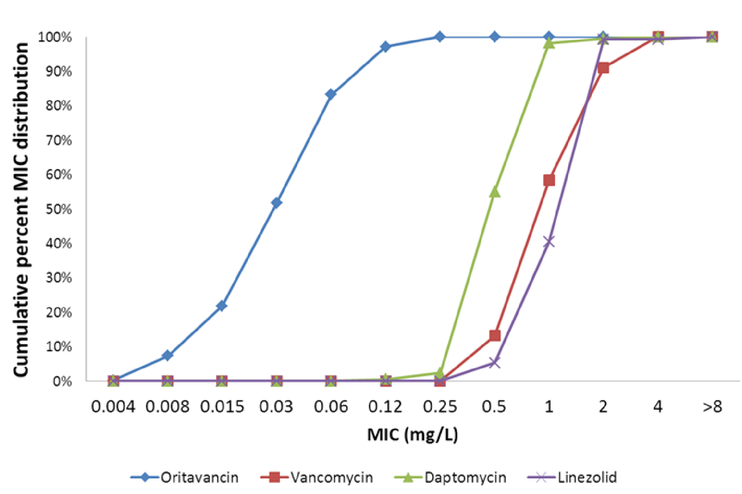

Figure 1. Cumulative MIC distribution for oritavancin, daptomycin, linezolid and vancomycin against all 381 methicillin-resistant staphylococci.

Conclusions

- Oritavancin showed potent activity against all methicillin-resistant staphylococci collected throughout Europe during 2011.
- Oritavancin was the most active agent tested.
- There was some evidence of resistance to newer agents such as tigecycline, daptomycin and linezolid, but this was mainly focused in Germany or Italy.

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