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Activity of oritavancin against methicillin-resistant staphylococci, vancomycin-resistant enterococci and β-haemolytic streptococci collected from western European countries in 2011

Ian Morrissey[1]*, Harald Seifert[2], Rafael Canton[3], Patrice Nordmann[4], Stefania Stefani[5], Alasdair MacGowan[6], Regina Janes[1] and Daniel Knight[1]† on behalf of the Oritavancin Study Group‡

[1]Quotient Bioresearch Ltd, Fordham, UK; [2]Institute for Medical Microbiology, Immunology, and Hygiene, University of Cologne, Cologne, Germany; [3]Servicio de Microbiología and CIBER en Epidemiología y Salud Pública (CIBERESP), Instituto Ramón y Cajal de Investigación Sanitaria (IRYCIS) and Hospital Universitario Ramón y Cajal, Madrid, Spain; [4]Hôpital de Bicêtre, Paris, France; [5]Department of Bio-Medical Science, Section of Microbiology, University of Catania, Catania, Italy; [6]Southmead Hospital, Bristol, UK

*Corresponding author. Present address: IHMA Europe Sàrl, 9A Route de la Corniche, 1066 Epalinges, Switzerland. Tel: +44-(0)1279-724929; E-mail: imorrissey@ihmainc.com

†Present address: The University of Western Australia, Queen Elizabeth II Medical Centre, Nedlands 6009 WA, Australia.

‡Members are listed in the Acknowledgements section.

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Objectives: To determine the activity of oritavancin against methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE) and β-haemolytic streptococci recently isolated from acute bacterial skin and skin structure infections or bacteraemia in western Europe.

Methods: Forty-one centres in Spain (8), Italy (9), Germany (8), France (8) and the UK (8) submitted 866 isolates [204 methicillin-resistant *Staphylococcus aureus* (MRSA), 177 methicillin-resistant coagulase-negative staphylococci (MRCoNS), 101 VRE, 193 *Streptococcus agalactiae* and 191 *Streptococcus pyogenes*] that were collected during the first 6 months of 2011. These were re-identified and susceptibilities to oritavancin and comparators were determined.

Results: Oritavancin was very active against MRSA (MIC_{50}/MIC_{90} 0.03/0.06 mg/L), MRCoNS (0.06/0.12 mg/L), VRE (0.03/0.06 mg/L), *S. agalactiae* (0.03/0.06 mg/L) and *S. pyogenes* (0.06/0.25 mg/L). The highest oritavancin MIC observed was 0.25 mg/L (species were *S. aureus*, *Staphylococcus epidermidis*, *Staphylococcus hominis*, *S. agalactiae*, *S. pyogenes* and *Enterococcus faecalis*).

Conclusions: These data from recently collected Gram-positive bacteria in western Europe confirm the potent *in vitro* activity of oritavancin against a wide range of resistant MRSA, MRCoNS and VRE isolates, including ones resistant to newer agents.

Keywords: Europe, lipoglycopeptides, Gram-positive bacteria

Introduction

Oritavancin is a semi-synthetic lipoglycopeptide currently in global Phase 3 clinical trials for the treatment of acute bacterial skin and skin structure infections (ABSSSIs). This novel compound has demonstrated clinical effectiveness in two previous Phase 3 trials.[1] Oritavancin is a promising new agent in the treatment of Gram-positive infections, including those caused by multidrug-resistant *Staphylococcus aureus*[2] and enterococci.[3]

This current study evaluated the *in vitro* activity of oritavancin and comparators against recently circulating methicillin-resistant staphylococci, vancomycin-resistant enterococci (VRE) and β-haemolytic streptococci from western Europe.

Materials and methods

A total of approximately 1000 isolates were sought from a target network of 41 collecting centres in France (8), Germany (8), Italy (9), Spain (8) and the UK (8) between 1 January 2011 and 30 June 2011. The target isolates ($n=25$) to be collected per centre were five each of methicillin-resistant *S. aureus* (MRSA), methicillin-resistant coagulase-negative staphylococci (MRCoNS), *Streptococcus pyogenes*, *Streptococcus agalactiae* and VRE. Isolates were re-identified by matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) or Lancefield grouping as required. Methicillin resistance in staphylococci was confirmed by cefoxitin disc screen as described by the CLSI.[4]

The MICs of oritavancin, vancomycin, teicoplanin, daptomycin, linezolid, tigecycline, tetracycline, ampicillin, clindamycin, levofloxacin and

trimethoprim/sulfamethoxazole were determined by broth microdilution methodology using dried panels supplied by TREK Diagnostics (East Grinstead, UK). The plates have been validated as equivalent to the approved CLSI testing method for oritavancin, which includes 0.002% polysorbate-80.[5] Zone diameters were determined for erythromycin, chloramphenicol, kanamycin, tobramycin and gentamicin following CLSI procedures.[4] Susceptibility to comparators was determined using breakpoints set by the CLSI.[6] No CLSI or EUCAST breakpoints are currently available for oritavancin.

Results

Isolate collection

A total of 866 Gram-positive isolates were collected, representing 86.6% of the target of 1000 isolates (Table 1). The shortfall was mainly due to difficulty in collecting eligible VRE isolates from France, Italy, Spain and the UK [$n=15$ (37.5%), $n=26$ (57.8%), $n=6$ (15.0%) and $n=16$ (40.0%), respectively]. The majority of the VRE isolates collected were vancomycin-resistant *Enterococcus faecium* and only 17 vancomycin-resistant *Enterococcus faecalis* isolates were collected (Table 1). A total of 492 isolates (57%) were from ABSSSIs and the remainder (374 isolates, 43%) were from bacteraemia (data not shown).

Summary of oritavancin activity

Cumulative distributions of the MICs of oritavancin for MRSA, MRCoNS, *S. pyogenes*, *S. agalactiae* and VRE are shown in Figure 1. Overall, the MIC_{50} and MIC_{90} of oritavancin were, respectively, 0.03 and 0.06 mg/L for MRSA, 0.06 and 0.12 mg/L for MRCoNS, 0.03 and 0.06 mg/L for VRE (predominantly *E. faecium*), 0.06 and 0.25 mg/L for *S. pyogenes* and 0.03 and 0.06 mg/L for *S. agalactiae*. Only a small number of vancomycin-resistant *E. faecalis* isolates were collected ($n=17$), but these resulted in a slightly higher oritavancin MIC distribution (MIC_{90} 0.25 mg/L) than vancomycin-resistant *E. faecium* isolates. Summary MIC and susceptibility data are shown in Table S1 (available as Supplementary data at *JAC* Online).

Activity against MRSA

Oritavancin inhibited all strains of MRSA at ≤0.25 mg/L (Figure 1), and all MRSA strains were fully susceptible to linezolid, vancomycin and teicoplanin. Against one isolate from Germany, the MIC of tigecycline was 0.5 mg/L (overall tigecycline susceptibility 99.5%), and against three isolates from Italy the MIC of daptomycin was 2 or 4 mg/L (overall daptomycin susceptibility 98.5%). MIC data for MRSA are shown in Table S1.

Activity against MRCoNS

Oritavancin inhibited all strains of MRCoNS at ≤0.25 mg/L (Figure 1). An analysis of MIC data for MRCoNS is given in Table S1. Six isolates of *Staphylococcus epidermidis* (one from Italy and five from Germany) were resistant to tigecycline (MIC >1 mg/L). Four isolates (one *Staphylococcus capitis* from Germany, two *S. epidermidis* from Germany and one *Staphylococcus pettenkoferi* from Italy) were daptomycin-non-susceptible (all MICs of 2 mg/L). Three *S. epidermidis* isolates (one from Spain and two from Italy) were resistant to linezolid (MIC >8 mg/L). Interestingly, the isolate from Spain showed a Cfr phenotype with co-resistance to clindamycin and chloramphenicol, but not erythromycin.

Table 1. Gram-positive bacteria collected from western European countries in 2011

	Country					
Pathogen	France	Germany	Italy	Spain	UK	All
MRSA	37	43	41	45	38	204
All MRCoNS	34	38	41	34	30	177
Staphylococcus capitis	1	2				3
Staphylococcus cohnii					1	1
Staphylococcus epidermidis	24	35	27	25	21	132
Staphylococcus haemolyticus	6	1	4	6	4	21
Staphylococcus hominis	3		7	3	3	16
Staphylococcus pettenkoferi			1		1	2
Staphylococcus warneri			2			2
All VRE	15	38	26	6	16	101
Enterococcus casseliflavus			1	2		3
Enterococcus faecalis		1	12		4	17
Enterococcus faecium	13	37	13	2	12	77
Enterococcus gallinarum				2		2
Enterococcus hirae	1					1
Enterococcus raffinosus	1					1
Streptococcus pyogenes	38	40	37	39	37	191
Streptococcus agalactiae	36	42	39	39	37	193

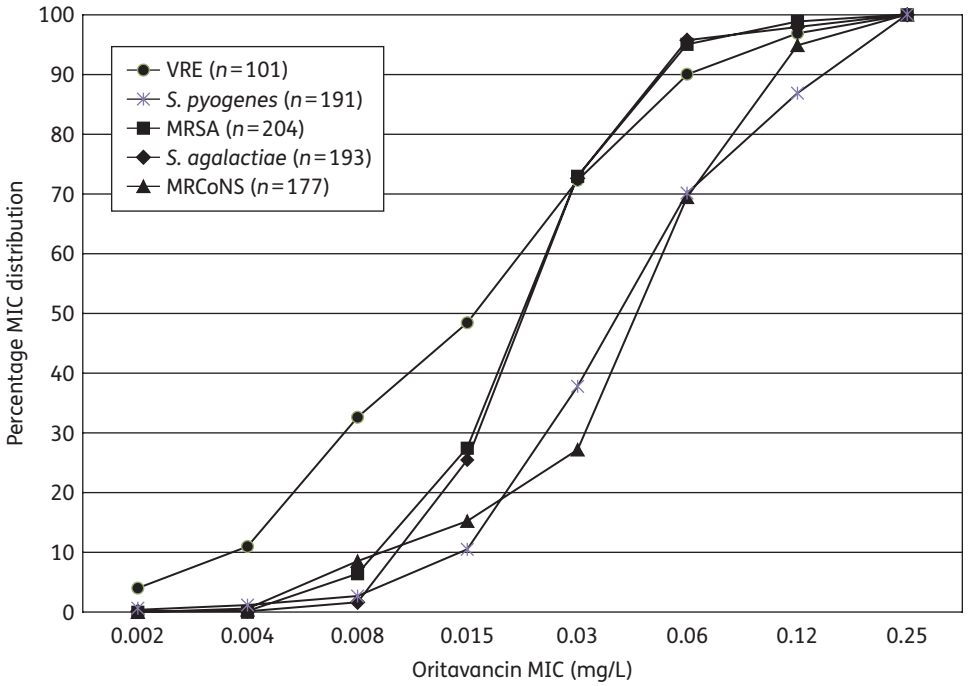

Figure 1. Cumulative distributions of the MICs of oritavancin for Gram-positive bacteria from European countries.

Activity against β-haemolytic streptococci

Oritavancin inhibited all strains of β-haemolytic streptococci at ≤0.25 mg/L (Figure 1). Resistance to antimicrobials by *S. pyogenes* was generally infrequent (≤1%); however, higher rates of resistance were seen to tetracycline (11.5%), erythromycin (7.3%) and chloramphenicol (2.1%) (Table S1). Resistance to most antimicrobials by *S. agalactiae* was also rare (≤0.5%); however, very high resistance was observed to tetracycline, at 81.9% for all countries combined, and some resistance was also found to erythromycin (22.8%), clindamycin (18.1%) and chloramphenicol (1.6%) (Table S1).

Activity against VRE

Oritavancin inhibited all strains of VRE at ≤0.25 mg/L (Figure 1). Twenty-two VRE strains retained susceptibility to teicoplanin (21.8%), suggesting that these isolates had a *vanB* genotype. Three linezolid-resistant *E. faecium* isolates were found in two sites in Germany (MIC >8 mg/L). Two isolates from France (one *E. faecium* and one *Enterococcus hirae*) were non-susceptible to daptomycin (MIC >4 mg/L). Three isolates of VRE [one from Germany (*E. faecalis*) and two from Italy (one *E. faecalis* and one *E. faecium*)] were non-susceptible to tigecycline (MIC 0.5 mg/L). More than 90% of VRE isolates were resistant to erythromycin or levofloxacin and more than 70% were resistant to co-trimoxazole or ampicillin. Overall, around 40%–50% of isolates were resistant to tetracycline or high-level gentamicin. Only chloramphenicol showed low-level resistance (5.9% overall) (Table S1).

Discussion

In summary, oritavancin showed potent activity against currently circulating methicillin-resistant staphylococci, VRE and β-haemolytic streptococci in western Europe. As a whole, Gram-positive isolates from France, Germany, Italy, Spain and the UK showed variable resistance to other antimicrobial agents that had no effect on the activity of oritavancin. These included MRCoNS and VRE isolates with high levels of resistance to most other antimicrobial agents and also isolates with decreased susceptibility to linezolid and daptomycin. The MIC of oritavancin was not greater than 0.25 mg/L for any strains of any organism group tested in this study. These data are virtually identical to those found in a previous study of European Gram-positive isolates collected between 2005 and 2008.[7] The exception was the activity of oritavancin against *S. agalactiae*; we found an MIC_{90} of 0.06 mg/L compared with a slightly higher MIC of 0.25 mg/L reported previously.[7] Our findings also complement the data of Mendes *et al.*,[3] who reported strong activity of oritavancin against US and European isolates of *vanA*-positive *E. faecium* and *vanA*-positive *E. faecalis*, albeit with a slightly higher MIC distribution for the latter.

There was evidence among the isolates collected from Europe of non-susceptibility and resistance to other agents, such as linezolid, daptomycin and tigecycline, albeit at relatively low rates. As a reduction in susceptibility to these newer agents is inevitable sooner or later, the introduction of oritavancin as a treatment option for Gram-positive bacterial infections would increase the number of drugs that are active against these pathogens.

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Members of the Oritavancin Study Group (who submitted isolates for this study)

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Transparency declarations

I. M. is a former employee of Quotient Bioresearch Ltd, which received funding to carry out the laboratory work from The Medicines Company and has received similar funding for laboratory work and consultancy from numerous other pharmaceutical companies. I. M.'s current employer is IHMA Europe Sàrl. H. S. has received research funding from Basilea, Novartis and Pfizer, has been a consultant for Astellas, AstraZeneca, Janssen-Cilag, Novartis and Wyeth, and has served on the speakers' bureaus of Astellas, Bayer, Gilead, Infectopharm, Janssen-Cilag, MSD, Novartis, Oxoid and Pfizer. R. C. has received research funding from Novartis and has participated in educational symposia organized by Novartis and Pfizer. S. S. has received research funding from Novartis and Pfizer, has been a consultant for Roche, Novartis and Pfizer, and has served on the speakers' bureaus of Novartis, BD and Pfizer. P. N., A. M., R. J. and D. K.: none to declare.

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