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

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Received 19 June 2012; returned 17 July 2012; revised 24 July 2012; accepted 27 July 2012

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 (MIC50/MIC90 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, S. 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. Oritavancin is a promising new agent in the treatment of Gram-positive infections, including those caused by multidrug-resistant Staphylococcus aureus and enterococci. 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.

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. Zone diameters were determined for erythromycin, chloramphenicol, kanamycin, tobramycin and gentamicin following CLSI procedures. Susceptibility to comparators was determined using breakpoints set by the CLSI. 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<sub>50</sub> and MIC<sub>90</sub> 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<sub>90</sub> 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>
<thead>
<tr>
<th>Table 1. Gram-positive bacteria collected from western European countries in 2011</th>
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<tr>
<td><strong>Pathogen</strong></td>
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<tr>
<td>MRSA</td>
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<tr>
<td>All MRSA</td>
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<tr>
<td><em>Staphylococcus capitis</em></td>
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<td><em>S. cohnii</em></td>
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<td><em>Staphylococcus epidermidis</em></td>
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<td><em>S. haemolyticus</em></td>
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<td><em>S. hominis</em></td>
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<td><em>S. pettenkoferi</em></td>
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<tr>
<td><em>S. warneri</em></td>
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<tr>
<td>All VRE</td>
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<tr>
<td><em>Enterococcus casseliflavus</em></td>
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<tr>
<td><em>E. faealis</em></td>
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<td><em>E. faecium</em></td>
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<td><em>E. gallinarum</em></td>
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<td><em>E. hirae</em></td>
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<td><em>E. raffinosus</em></td>
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<td><em>Streptococcus pyogenes</em></td>
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<td><em>S. agalactiae</em></td>
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</tbody>
</table>
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. The exception was the activity of oritavancin against S. agalactiae; we found an MIC90 of 0.06 mg/L compared with a slightly higher MIC of 0.25 mg/L reported previously. Our findings also complement the data of Mendes et al., 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.

Acknowledgements

These data were presented in part at the 22nd ECCMID, London, UK, 2012 (Abstract P1883).

We would like to thank Joanna Soltysiak and Alex Smith for their technical support.
Members of the Oritavancin Study Group (who submitted isolates for this study)

Professor R. Bonnet, Gabriel Montpeid, France; Professor C. J. Soussy, Mondor Creteil, France; Professor R. Courcol, Lille, France; Professor R. Leclercq, Caen, France; Dr R. Zahar, Paris, France; Dr Y. Rio, Metz, France; Professor C. Payart, Paris, France; Professor M. Abele-Horn, Würzburg, Germany; Professor W. Pfister, Jena, Germany; Dr C. Schoerner/Dr F. Albert, Erlangen, Germany; Professor E. Jacobs, Dresden, Germany; Dr S. Schubert, Kiel, Germany; Professor R. Mutters, Marburg, Germany; Professor F-J Schmitz, Minden, Germany; Dr F. Luzzano, Lecco, Italy; Dr E. Manso, Ancona, Italy; Dr C. Scarparo, Udine, Italy; Professor G. Fadda, Roma, Italy; Professor F. Rossano, Napoli, Italy; Professor G. M. Rossolini, Siena, Italy; Dr G. P. Gesu, Milan, Italy; Professor M. P. Landini, Bologna, Italy; Dr L. Martinez, Santander, Spain; Dr J. L. Pérez, Mallorca, Spain; Dr C. Gimeno, Valencia, Spain; Dr A. Pascual, Sevilla, Spain; Dr J. Lihares, Llobrigat, Spain; Dr R. Bartolomé, Barcelona, Spain; Dr R. Cisterna, Bilbao, Spain; Professor K. Gould, Newcastle, UK; Dr M. Dryden, Winchester, UK; Dr M. Weinbren, Coventry, UK; Dr A. Swann, Leicester, UK; Professor M. Wilcox, Leeds, UK; Dr G. Moore, London, UK; Mrs J. Andrews/Ms J. Ashby, Birmingham, UK; and Dr S. Kaul, Harefield, UK.

Funding

This work was supported by educational/research grants from The Medicines Company.

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 Sarl. 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.

References


