P 1644

Activity of Oritavancin (ORI) against European Gram-Positive Bacterial Pathogens Associated with Skin/Wound Infections and Bacteremia

Contact info:
Jennifer Deane, B.S.
Tel: 703-480-2608
Email: jenniferdeane@eurofins.com

J Deane[1], C Opiela[1], D Shah[1], G Moeck[2], F Arhin[2], D F Sahm[1]

[1]Eurofins, Chantilly, VA, USA; [2]The Medicines Company, Parsippany, NJ, USA

Abstract (Amended)

Objective. Oritavancin (ORI) is a semisynthetic lipoglycopeptide in Phase 3 clinical development for the treatment of complicated skin and soft tissue infections. We evaluated ORI activity, relative to that of vancomycin (VAN) and 11 other comparators, against currently-circulating Gram-positive pathogens from patient specimen sources relevant to the Phase 3 studies that are presently underway.

Methods. 756 single-patient, non-consecutive *Staphylococcus aureus* (SA) and 163 beta-haemolytic streptococcal (BHS) isolates were collected in 2011-2012 from 9 sites distributed across Europe. Each bacterial isolate was sub-cultured for inoculum preparation and was subjected to broth microdilution testing and in accordance with CLSI M7. Results were interpreted using EUCAST breakpoints. From the resulting database, this analysis focused on the activities of ORI and VAN against blood and skin/wound isolates.

Results. The following table shows ORI and VAN activity according to specimen source.

			ORI (mg/L)			VAN (mg/L)		
Organism	Infection Site	N	Mode	MIC $_{50}$	MIC $_{90}$	Mode	MIC $_{50}$	MIC $_{90}$
All SA	Skin/Wound	323	0.03	0.03	0.06	0.5	0.5	1
	Blood	135	0.03	0.03	0.06	0.5	0.5	1
	Other/Unknown	298	0.03	0.03	0.06	0.5	0.5	1
MRSA[1]	Skin/Wound	50	0.03	0.03	0.12	0.5	0.5	1
	Blood	32	0.03	0.03	0.12	0.5	0.5	1
	Other/Unknown	97	0.03	0.03	0.12	0.5	0.5	1
MSSA[1]	Skin/Wound	273	0.03	0.03	0.06	0.5	0.5	1
	Blood	103	0.03	0.03	0.06	0.5	0.5	1
	Other/Unknown	201	0.03	0.03	0.06	0.5	0.5	1
BHS[2]	Blood	48	0.06	0.06	0.25	0.25	0.25	0.5
	Skin/Wound	58	0.06	0.06	0.25	0.25	0.25	0.5
	Other/Unknown	57	0.06	0.06	0.25	0.25	0.25	0.5

[1] MRSA: methicilllin-resistant S. aureus, MSSA: methicillin-susceptible S. aureus

[2] 77 S. agalactiae, 78 S. pyogenes, 1 Streptococcus Group C, 7 Streptococcus Group G

Conclusions. These findings demonstrate that against both SA (both MRSA and MSSA) and BHS, ORI maintained a comparable and high level of *in vitro* activity regardless of the clinical source of the pathogen. This level of activity was several-fold more potent than VAN, and underscores the strong potential ORI has for the treatment of infections caused by currently-circulating Gram-positive pathogens.

Introduction

ORI is a semi-synthetic lipoglycopeptide with activity against a wide range of Gram-positive bacteria, including organisms that are resistant to vancomycin and other drug classes. ORI is currently in clinical development for the treatment of skin and soft tissue infections. Pre-launch surveillance of new agents provides a benchmark against which post-launch surveillance trends could be compared. A key group of organisms against which ORI would be useful is Gram-positive pathogens exhibiting problematic resistance phenotypes. This purpose of this study was to determine if there were any trends in ORI and VAN activity according to the infection site (bacteraemia and skin/wound infections).

Methods

- Single patient, non-consecutive, clinical isolates of *S. aureus* (SA) and beta-haemolytic streptococci (BHS), totaling 756 and 163, respectively, were collected in 2011-2012 from 9 sites distributed across Europe (United Kingdom, Spain, Italy, and Germany).
- A majority (71%) of the Other/Unknown specimen category were respiratory isolates. The remaining organisms were isolated from various other sources (urine, eye, cerebral spinal fluid, etc.).
- BHS isolates consisted of 77 *S. agalactiae*, 78 *S. pyogenes*, 1 *Streptococcus* Group C, and 7 *Streptococcus* Group G.
- Identification of species was confirmed at Eurofins and MICs of ORI, VAN and other comparators were determined by broth microdilution according to CLSI M7 guidelines. Broth microdilution panels were provided by ThermoFisher Scientific (Cleveland, OH).
- Although several antimicrobials were tested, this analysis focused on the activity trends for VAN and ORI.

Results–1

Table 1. ORI and VAN Activity According to Specimen Source

			ORI (mg/L)			VAN (mg/L)		
Organism	Infection Site	N	Mode	MIC $_{50}$	MIC $_{90}$	Mode	MIC $_{50}$	MIC $_{90}$
All SA	Skin/Wound	323	0.03	0.03	0.06	0.5	0.5	1
	Blood	135	0.03	0.03	0.06	0.5	0.5	1
	Other/Unknown	298	0.03	0.03	0.06	0.5	0.5	1
MRSA[1]	Skin/Wound	50	0.03	0.03	0.12	0.5	0.5	1
	Blood	32	0.03	0.03	0.12	0.5	0.5	1
	Other/Unknown	97	0.03	0.03	0.12	0.5	0.5	1
MSSA[1]	Skin/Wound	273	0.03	0.03	0.06	0.5	0.5	1
	Blood	103	0.03	0.03	0.06	0.5	0.5	1
	Other/Unknown	201	0.03	0.03	0.06	0.5	0.5	1
BHS[2]	Blood	48	0.06	0.06	0.25	0.25	0.25	0.5
	Skin/Wound	58	0.06	0.06	0.25	0.25	0.25	0.5
	Other/Unknown	57	0.06	0.06	0.25	0.25	0.25	0.5

[1] MRSA: methicilllin-resistant S. aureus, MSSA: methicillin-susceptible S. aureus

[2] 77 S. agalactiae, 78 S. pyogenes, 1 Streptococcus Group C, 7 Streptococcus Group G

Figure 1A-B. ORI and VAN MIC Distributions for All Evaluated *S. aureus* According to Methicillin Phenotype

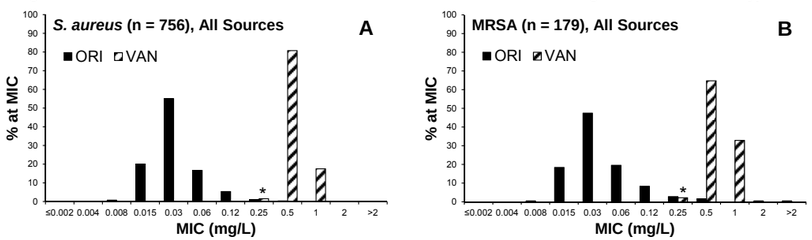


Figure 2A-B. ORI and VAN MIC Distributions for All Evaluated *S. aureus* Isolated from Skin/Wound Infections According to Methicillin Phenotype

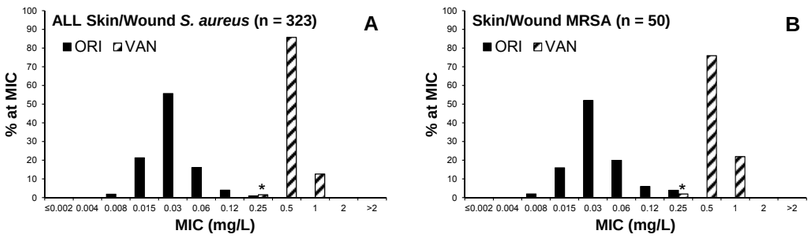
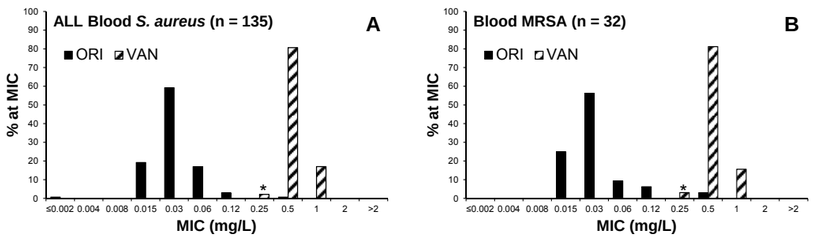


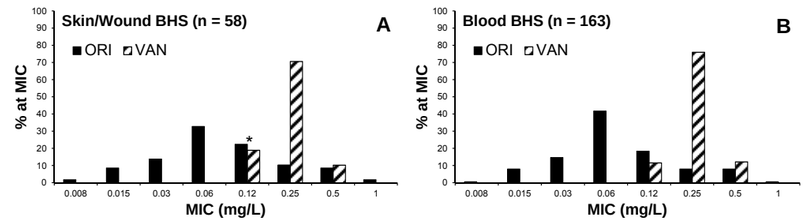
Figure 3A-B. ORI and VAN MIC Distributions for All Evaluated *S. aureus* Isolated from the Bloodstream According to Methicillin Phenotype



** VAN was tested between 0.25 mg/L and 32 mg/L against S. aureus*

Results–2

Figure 4A-B. ORI and VAN MIC Distributions for all Evaluated Beta-Haemolytic Streptococci According to Specimen Source



** VAN was tested between 0.06 mg/L and 1 mg/L against BHS*

Table 1.

- Regardless of specimen source and phenotype (MRSA vs. MSSA), ORI was several-fold more potent than VAN.
- Among MRSA for all specimen source groups, the ORI MIC$_{90}$s were consistently 0.12 mg/L, while those for VAN were 1 mg/L.
- Among MSSA the ORI MIC$_{90}$s were consistently 0.06 mg/L, while those for VAN were 1 mg/L.
- For BHS, ORI MIC$_{90}$s for all specimen source groups were consistently 0.25 mg/L while those for VAN were 0.5 mg/L.

Figure 1A - B.

- The ORI and VAN MIC distributions obtained for all *S. aureus* encountered in the study showed that the mode for ORI was 0.03 mg/L and that the percentage of strains at that mode was comparable between all *S. aureus* and MRSA.
- While the VAN MIC mode was 0.5 mg/L for both populations, the percentage of strains with MICs of 1 mg/L increased from 17.6% among all *S. aureus* to 33 % among MRSA.

Figure 2A – B.

- For skin/wound isolates, the ORI and VAN MIC distributions obtained for all *S. aureus* encountered in the study showed that the mode for ORI was 0.03 mg/L and that the percentage of strains at that mode was comparable between all *S. aureus* and MRSA.
- While the VAN MIC mode was 0.5 mg/L for both populations, the percentage of strains with MICs of 1 mg/L increased from 12.7% among all *S. aureus* to 22% among MRSA.
- The other group of *S. aureus* that showed a differences in VAN MIC = 1mg/L rates between all isolates and MRSA were those from the various other body sources, or for which the source was not provided (data not shown). Within this group, 23.2% of all *S. aureus* had VAN MIC = 1 mg/L while 44.3% of MRSA had VAN MIC = 1 mg/L.

Figure 3A – B.

- For blood isolates, the ORI and VAN MIC distributions obtained for all *S. aureus* encountered in the study showed that the mode for ORI was 0.03 mg/L and that the percentage of strains at that mode was comparable between all *S. aureus* and MRSA.
- The VAN MIC mode was 0.5 mg/L for both populations and the percentage of strains with MICs of 1 mg/L were comparable between all *S. aureus* (17%) and MRSA (15%).

Figure 4A – B.

- Among BHS, the ORI and VAN MIC distributions overlapped somewhat for both skin/wound and blood isolates. ORI's modal MIC among organisms from both specimen sources (0.06 mg/L) was two doubling dilutions lower than the VAN modal MICs of 0.25 mg/L.

Summary and Conclusions

These findings demonstrated that against *S. aureus* (including MRSA) and BHS from various specimen sources, ORI maintained a comparable and high level of *in vitro* activity. This level of activity was several-fold more potent than VAN, and underscores the strong potential ORI has for the treatment of infections caused by currently-circulating Gram-positive pathogens. Also of interest was the increased prevalence of MRSA, from certain body sites, with VAN MIC = 1 mg/L. This potential trend should be monitored carefully.

References

CLSI. 2012. CLSI document M7-A9.
EUCAST. 2013. Breakpoint tables for interpretation of MICs and zone diameters. Version 3.1 http://www.eucast.org.