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Assessment of the Propensity of Oritavancin to Induce Susceptibility Changes Among *Staphylococcus aureus* Nasal Carriage Isolates in a Phase 2 Study in Patients with Acute Bacterial Skin and Skin Structure Infections

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Abstract

Objective: The lipoglycopeptide oritavancin (ORI) is approved for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) due to gram-positive organisms including methicillin-resistant *S. aureus* (MRSA). Whether the long terminal half-life of lipoglycopeptides in serum following IV administration is associated with emergence of resistance in normal bacterial flora is unknown. This study determined the susceptibility to ORI and vancomycin (VAN) of pairs of *S. aureus* isolates from nasal swabs at baseline and post-baseline in a Phase 2 study of IV ORI for treatment of ABSSSI.

Methods: Study SD001 was a Phase 2 multicenter, randomized, double-blind efficacy and safety study of ORI in adults with ABSSSI. Patients received IV ORI either as a 1200 mg dose, 200 mg once daily for 3-7 days, or 800 mg on Day 1 plus 400 mg on Day 5, at the Investigator's discretion. Nasal swabs were collected from patients at baseline and at the Test-of-Cure (ToC) visit (Day 21-29). *S. aureus* isolates cultured from swabs locally were sent to a central laboratory for susceptibility testing against ORI, VAN and other comparators by broth microdilution (CLSI M7).

Results: Overall, 124 patients had nasal swabs performed at baseline and ToC. A total of 29 pairs (baseline and ToC) of *S. aureus* isolates, 44.8% of which were MRSA, were available for confirmatory susceptibility testing. The median interval between baseline and ToC visit in these 29 patients was 22 days. ORI MIC range (0.015-0.12 µg/mL; 100% susceptible) and MIC_{50}/MIC_{90} (0.03/0.06 µg/mL) were identical for baseline and ToC isolates. VAN MIC range (0.25-1/2 µg/mL; 100% susceptible) and MIC_{50}/MIC_{90} (0.5/1 µg/mL) were within 2-fold for baseline and ToC isolates. ORI and VAN MICs of all ToC isolates were within 2-fold of respective MICs of the corresponding isolate at baseline.

Conclusions: In this Phase 2 study, one quarter of tested patients carried *S. aureus* in the anterior nares both at baseline and at ToC. ORI and VAN MICs of *S. aureus* isolates from ToC were within 2-fold of the MICs of the corresponding baseline isolates, suggesting that IV ORI treatment was not associated with changes in susceptibility to either ORI or VAN among nasal carriage isolates of *S. aureus* in patients with ABSSSI in this study.

Background

Emergence of colonizing microorganisms with decreased antibiotic susceptibility has been described following systemic treatment with amoxicillin-clavulanic acid and telithromycin[1] and has also been inferred to occur with linezolid treatment[2]. We investigated whether IV oritavancin treatment of ABSSSI patients in a Phase 2 study[3] was associated with susceptibility changes amongst *S. aureus* isolates cultured from the nares.

Methods

Study SD001 was a Phase 2 multicenter, randomized, double-blind study of oritavancin in adults with ABSSSI[3]. Patients received IV oritavancin as one of the following dosage regimens: Single, single 1200 mg dose; Daily, 200 mg once daily for 3-7 days; Infrequent, 800 mg on Day 1 plus an optional 400 mg on Day 5 as determined by the blinded Investigator, based on clinical criteria.

Patients were enrolled at 43 sites in 5 countries (Australia, India, Romania, Ukraine, and the US) between September 2007 and April 2008. The study was approved by site-specific ethics review boards and all patients provided informed consent.

Whereas the main objectives of the study were to determine the efficacy and safety of each dosage regimen, an additional objective was to evaluate whether IV treatment with oritavancin led to susceptibility changes amongst post-treatment isolates of *S. aureus* collected from the nose, as representatives of normal colonizing microbial flora.

Nasal swabs were collected from patients at baseline and at the Test of Cure (ToC) visit on Day 21-29. *S. aureus* isolates that were cultured from swabs at the local laboratory by standard microbiological procedures were sent to a central laboratory (Covance Clinical Development Services, Princeton, NJ) for confirmation of identity and susceptibility testing against oritavancin, vancomycin and other comparators by broth microdilution following CLSI M7 guidelines which, for oritavancin, require use of 0.002% polysorbate-80. MRSA was confirmed by cefoxitin disk testing.

There is no pharmacological information regarding the presence of oritavancin in the nasal secretions of patients in this study.

Results

A total of 124 *S. aureus* isolates were initially recovered from nasal swabs from patients in the Phase 2 study SD001 (Table 1).

Table 1. Recovery of *S. aureus* from nasal swab culture, by treatment group

	200 mg ORI Daily Dose (N=43) n (%)		1200 mg ORI Single Dose (N=44) n (%)		800 mg ORI Infrequent Dose (N=37) n (%)		Total (N=124) n (%)	
***S. aureus* isolated at Baseline visit?**	***S. aureus* isolated at Test of Cure visit?**							
	Yes	**No**	**Yes**	**No**	**Yes**	**No**	**Yes**	**No**
Yes	16 (80.0)	4 (20.0)	8 (53.3)	7 (46.7)	11 (64.7)	6 (35.3)	35 (67.3)	17 (32.7)
No	7 (30.4)	16 (69.6)	6 (20.7)	23 (79.3)	2 (10.0)	18 (90.0)	15 (20.8)	57 (79.2)

The median interval between Baseline and Test of Cure nasal swabs was 22 days (Table 2).

Table 2. Interval between Baseline and Test of Cure visit for recovery of *S. aureus* from nasal swab culture

Patients with *S. aureus* isolated from nasal swab at Test of Cure visit and having confirmed MIC (n)	**Study Day of ToC visit (days)**			
	Range	**Mean**	**Median**	**S.D.**
All (47)	15 - 31	22.7	22	2.8
Subset with corresponding nasal swab isolate from Baseline visit (29)	15 - 29	22.6	22	2.7

S.D., standard deviation

Results

Figure 1. Process to isolate and characterize *S. aureus* from nasal swab culture and corresponding rates of recovery in Phase 2 study SD001

S. aureus was isolated from 124/545 nasal swabs at the local laboratories, yielding a recovery rate of 22.7%. In total, 118 of these isolates were available for confirmatory identification and susceptibility testing at the central laboratory. Overall, 57/118 (48.3%) of these isolates were MRSA:

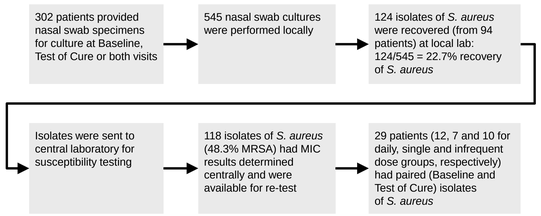


Figure 2. Oritavancin and vancomycin MIC distribution against *S. aureus* isolates from nasal swab culture (n=118)

Oritavancin exhibited potent in vitro activity against the tested isolates of *S. aureus*, with MIC_{50} = 0.03 µg/mL and MIC_{90} = 0.12 µg/mL. Overall, 99.2% of isolates were susceptible to oritavancin at the FDA[4], CLSI[5] and EUCAST[6] breakpoint of S ≤0.12 µg/mL. All isolates were susceptible to vancomycin (MIC_{50} = 1 µg/mL; MIC_{90} = 1 µg/mL).

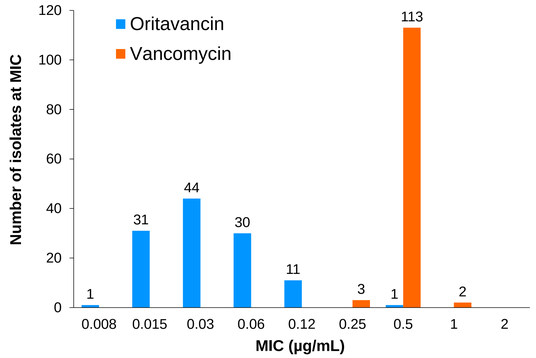


Figure 3. Oritavancin MICs of paired isolates of *S. aureus* from nasal swabs at Baseline and Test of Cure (n=58 isolates from 29 patients)

The oritavancin MICs of paired isolates (from baseline and Test of Cure visits within the same patient) were within one doubling dilution of one another.

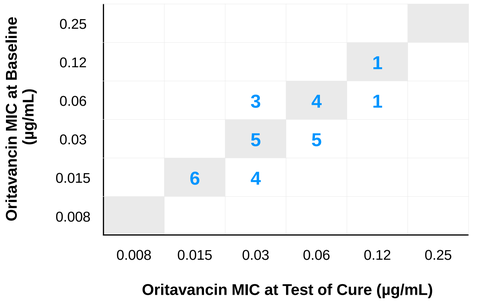
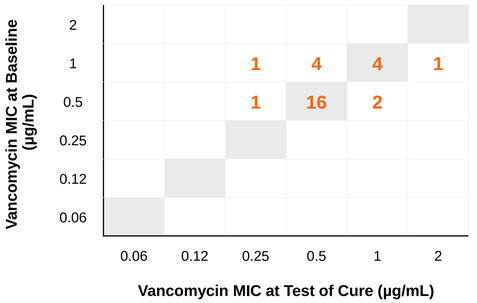


Figure 4. Vancomycin MICs of paired isolates of *S. aureus* from nasal swabs at Baseline and Test of Cure (n=58 isolates from 29 patients)

Similarly, the vancomycin MICs of isolates from the Test of Cure visit were not more than one doubling dilution higher than the vancomycin MIC of the corresponding isolate from the Baseline visit.



Conclusions

- Nasal carriage of *S. aureus* was common in this Phase 2 study in adult patients with ABSSSI, as approximately one quarter of tested patients carried *S. aureus* in the anterior nares at Baseline, Test of Cure or both visits
- MRSA was common, representing almost half of all *S. aureus* isolates recovered from nasal swabs
- Of the 118 *S. aureus* nasal swab isolates that were available for susceptibility testing at the central laboratory, 99.2% and 100% were susceptible to oritavancin and vancomycin, respectively. By MIC_{90}, oritavancin was 8-fold more potent than vancomycin against this collection of isolates
- Oritavancin MICs of post-treatment isolates (as collected at the Test of Cure visit approximately 3 weeks after initiation of therapy) were within one doubling dilution of MICs of the corresponding isolate from the Baseline visit. Similarly, vancomycin MICs of post-treatment isolates were not more than one doubling dilution higher than those of the corresponding Baseline isolate
- In adult patients with ABSSSI in this Phase 2 study, neither IV oritavancin treatment nor IV vancomycin treatment was associated with changes in susceptibility among nasal carriage isolates of *S. aureus*

Disclosures

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References

1. Crémieux AC, Muller-Serieys C, Panhard X, Delatour F, Tchimichkian M, Mentre F, Andremont A. Emergence of resistance in normal human aerobic commensal flora during telithromycin and amoxicillin-clavulanic acid treatments. Antimicrob Agents Chemother. 2003 Jun;47(6):2030-5.
2. Potoski BA, Adams J, Clarke L, Shutt K, Linden PK, Baxter C, Pasculle AW, Capitano B, Peleg AY, Szabo D, Paterson DL. Epidemiological profile of linezolid-resistant coagulase-negative staphylococci. Clin Infect Dis. 2006 Jul 15;43(2):165-71.
3. Dunbar LM, Milata J, McClure T, Wasilewski MM; SIMPLIFI Study Team. Comparison of the efficacy and safety of oritavancin front-loaded dosing regimens to daily dosing: an analysis of the SIMPLIFI trial. Antimicrob Agents Chemother. 2011 Jul;55(7):3476-84.
4. Prescribing information—ORBACTIV® (oritavancin) for injection. The Medicines Company, Parsippany (NJ). January 2016. http://www.orbactiv.com/pdfs/orbactiv-prescribing-information.pdf
5. Clinical and Laboratory Standards Institute (CLSI) M100-S26. Performance Standards for Antimicrobial Susceptibility Testing; Twenty-Sixth Informational Supplement. January 2016.
6. European Committee for Antimicrobial Susceptibility Testing (EUCAST). Breakpoint tables for interpretation of MICs and zone diameters. Version 6.0, 2016. http://www.eucast.org/fileadmin/src/media/PDFs/EUCAST_files/Breakpoint_tables/v_6.0_Breakpoint_table.pdf

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