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REAL-WORLD EFFICACY AND SAFETY OF ORITAVANCIN MULTIPLE DOSE TREATMENT IN PATIENTS WITH COMPLICATED GRAM-POSITIVE INFECTIONS

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ABSTRACT

- **Background:** Oritavancin (ORI) is a long-acting lipoglycopeptide antibiotic indicated for the treatment of adult patients with acute bacterial skin and skin structure infections caused or suspected to be caused by susceptible gram-positive (GP) pathogens. Clinicians rely on real-world studies to help guide therapeutic decision-making.
- **Methods:** Data collected from a retrospective observational program (2014-7), Clinical and Historic Registry and Orbactiv Medical Evaluation (CHROME), describes the utilization, outcomes, and adverse events (AEs) associated with ORI in 440 patients treated at 26 U.S. sites. We present data on a cohort of patients who received > 1 dose of ORI for complicated GP infections defined as receipt of ORI separated by no more than 14 d.
- **Results:** Thirty-two patients received 2 to 10 doses (mean, 3.3 doses) of ORI. Infections included bone and joint (n=11, including 8 with osteomyelitis), cellulitis (n=10), wound (n=8), abscess (n=2), and burn (n=1). Rate of AEs was low (6.3%). Monomicrobial infections were documented in 20 patients; MRSA and MSSA predominated (60% combined). All patients received 1200 mg ORI over 3 hrs except one patient who experienced an infusion-related AE and was switched to linezolid. A second patient experienced mild nausea which resolved following completion of the infusion. Patients received prior antibiotic therapy (22, 69%) immediately prior to ORI. Clinical response was observed in 30 of 32 patients (93.8%) overall, including 10 of 11 patients (90.9%) with bone and joint infections and 7 of 8 (87.5%) patients with osteomyelitis specifically. Definitive confirmation of microbiologic outcome through post-therapy C&S was rare according to clinical practice at the site.
- **Conclusions:** We describe the largest multi-center, retrospective, observational study in patients that received > 1 dose of ORI for the treatment of patients with complicated GP infections. This study further confirms that ORI is an effective and well-tolerated long-acting lipoglycopeptide antibiotic.

INTRODUCTION

- Oritavancin (Orbactiv; Melinta Therapeutics, Morristown, NJ) is a bactericidal long-acting lipoglycopeptide antibiotic approved in the US for the treatment of adult patients with ABSSSI caused by designated gram-positive pathogens including MRSA on the basis of 2 Phase 3 studies, SOLO I and SOLO II.[1-3]
- The consistently demonstrated safety and efficacy of oritavancin used for ABSSSI has stimulated some clinical experimentation with multiple dose regimens for treatment of complicated and deep-seated gram-positive infections. Several patient cases and case series describe the use of oritavancin in multiple-dose regimens for the treatment of bone and joint infections, pneumonia, bacteremia, and complicated surgical site infections.[4-9]
- An interim analysis of CHROME results have been reported for 112 patients.[10] These cases included oritavancin prescribed as a single dose for major types of ABSSSI.

METHODS

- Patients who received at least one dose of oritavancin were eligible for inclusion. Each site enrolled at least 15 consecutive patients between October 2014 and October 2017. Data collection procedures are described elsewhere.[10]
- To be included, patients had to (1) be treated with oritavancin for a suspected or confirmed gram-positive infection, and (2) have received the last dose of oritavancin at least 60 days prior to data entry into the electronic case report form (eCRF). Safety definitions were established prior to patient enrollment and included in the study protocol. Safety data were collected up to 60 days following the last dose of oritavancin.
- Clinical categories of efficacy were assessed between end of infusion of last dose plus 30 days. Clinical categories of efficacy were defined as one of the following: clinical cure (clinical signs and symptoms resolved), clinical improvement (partial resolution of clinical signs and symptoms); clinical failure (inadequate resolution, or new or worsening clinical signs and symptoms.
- A cohort of 32 patients received 2 to 10 ORI doses separated by no more than 14 d for complicated GP infections. This cohort was described in this report.

RESULTS

- In the CHROME program there 438 evaluable treatment courses in 440 unique patients. Overall, clinical response rates were 88.4% (342/387) and 86.3% (44/51) in patients receiving single dose and multiple dose courses, respectively.
- Twenty-two of 32 multi-dose patients (69%) received prior therapy, consisting predominantly of vancomycin (11/21, 52%) targeting suspected or documented gram-positive pathogens. Clinical improvement on prior therapies was documented in 7 (31.8%) patients.
- Twenty-two patients (69%) had a confirmed microbiologic culture for at least one gram-positive pathogen. The most common organism associated with monomicrobial infections was *Staphylococcus aureus* (12/20, 60%) and consisted of 4 cases with MSSA and 8 of MRSA. Two mixed infections included MSSA and *Streptococcus pyogenes* and another case with both MSSA and MRSA.
- In the cohort of interest, favorable clinical response was observed in 30 of 32 patients (93.8%), including 10 of 11 patients (90.9%) with bone and joint infections and 7 of 8 (87.5%) patients with osteomyelitis specifically. The clinical failure in a non-BJI case was a patient with a traumatic wound infection and microbiological persistence of *Corynebacterium striatum*.
- In the safety evaluable population of 440 patients, the overall rate of AEs was 6.9%. AEs leading to discontinuation were low (1.3%); serious or severe AEs were observed in 3 patients (0.7%). In the 32 patient cohort receiving multiple doses of oritavancin, AEs were reported in 2 (6.3%) patients. One patient experienced mild nausea; a second patient had an infusion-related reaction which was moderate and not serious. This patient was sent to the ED for observation but was discharged shortly thereafter.

RESULTS

TABLE. Patients treated with multiple-dose oritavancin for complicated gram-positive infections

Age/ Sex	Infection	Pathogen(s)	Oritavancin Dosing	Site(s) of Infusion	Clinical Outcome, ORI	Adverse Events, ORI	Reason For Entry/Prior Therapy
46/M	Osteomyelitis	MSSA, *S. pyogenes*	1200mg x 6 every 6-8 d	HOIC	Cure	None	Prior amoxicillin therapy failure
74/F	Cellulitis, nonpurulent	MRSA	1200mg x 2 every 11d	POIC	Cure	None	Prior doxycycline and VAN failure
47/F	Osteomyelitis	MRSA	1200mg x 2 every 9d	POIC	Failure	None	No prior therapy; ORI changed to doxycycline; amputation
86/F	Cellulitis, nonpurulent	MSSA	1200mg x 2 every 14d	POIC	Improvement	None	No prior therapy
70/F	Osteomyelitis	MRSA	1200mg x 10 every 7-8d	OP-HOU	Improvement	None	No prior therapy
75/M	Cellulitis, nonpurulent	Not cultured	1200mg x 2 every 14d	POIC	Cure	None	No prior therapy
60/F	Cellulitis, purulent with surgical wound	Coag-neg staph	1200mg x 4 every 7-17d	OP-HOU	Improvement	None	Prior VAN therapy with AE; change to ORI
78/F	Abscess, surgical wound	MRSA	1200mg x 2 every 14d	POIC	Cure	None	Prior VAN therapy with improvement
67/F	Cellulitis, purulent	*S. pyogenes*	1200mg x 6 every 7-8d	HOIC	Cure	None	Prior cefadroxil therapy failure
82/M	Cellulitis, nonpurulent	Not cultured	1200mg x 2 every 13d	POIC	Improvement	None	Prior PTZ and VAN therapy failure
50/F	Cellulitis, nonpurulent	Not cultured	1200mg x 2 every 14d	POIC	Cure	None	No prior therapy
67/M	Unspecified wounds	Coag-neg staph	1200mg x 7 every 6-8d	OP-HOU	Cure	None	Prior amoxicillin/clavulanate failure
60/M	Surgical wound	*E. faecalis*	1200mg x 2 every 14d	HOIC	Improvement	None	Prior amoxicillin and TMP/SMX failure
56/M	Traumatic wound	*Corynebacterium* sp.	1200mg x 3 every 14d	OP-HOU	Failure	None	No prior therapy; micro persistence
46/F	Abscess	MRSA	1200mg x 2 every 14d	HOIC	Cure	None	Prior tedizolid with improvement; relapsed necessitating ORI therapy
70/M	Osteomyelitis	*S. pyogenes*	1200mg x 2 every 6d	HOIC	Cure	None	Prior cephalexin failure, changed to DAL with AE necessitating change to ORI
57/M	Surgical wound	*Corynebacterium* sp.	1200mg x 6 every 6-8d	OP-HOU	Improvement	None	No prior therapy
66/M	Wound, unspecified	MSSA	1200mg x 2 every 8d	OP-HOU	Cure	None	Prior TMP/SMX failure
43/F	Native septic arthritis/synovitis	Culture-negative	1200mg x 5 every 6-14d	OP-HOU	Improvement	None	No prior therapy
55/F	Osteomyelitis	Culture-negative	1200mg x 3 every 14d (with oral TMP/SMX)	POIC	Cure	None	Prior cefazolin. daptomycin, linezolid, PTZ, and VAN failures
60/F	Surgical wound	Not cultured	1200mg x 2 every 11d	IP, then HH	Cure	None	No prior therapy
36/F	Osteomyelitis	MSSA	1200mg x 2 every 14d	POIC	Cure	None	Prior A/S, cefazolin, cephalexin, CFTX, TMP/SMX failures
31/M	Surgical wound	MSSA	1200mg x 2 every 14d	POIC	Cure	None	Prior VAN therapy changed to ORI for MSSA
24/M	Surgical wound	MRSA, MSSA	1200mg x 9 every 6-7d	ED	Cure	Mild nausea	Prior CFTX, clinda, nafcillin, VAN failure
58/M	Osteomyelitis, left foot	MRSA	1200mg x 1, then partial dose in 14d	POIC	Improvement	Infusion-related reaction	Prior minocycline, VAN failure; change to linezolid following ORI AE
22/M	Septic arthritis/synovitis	*Bacillus* sp	1200mg x 2 every 14d	IP, then ED	Cure	None	Prior cefazolin failure followed by VAN improvement
51/M	Infected burn	Not cultured	1200mg x 2 every 7d	HOIC	Improvement	None	Prior cefepime, VAN therapy improvement; limb amputation still required
48/M	Cellulitis, nonpurulent	Not cultured	1200mg x 2 every 14d	POIC	Cure	None	Prior telavancin with improvement
86/F	Cellulitis, nonpurulent	MRSA	1200mg x 2 every 14d	POIC	Cure	None	No prior therapy
46/F	Osteomyelitis, skull	MRSA	1200mg x 6 every 7-14d	ED	Cure	None	Prior VAN therapy with improvement
78/M	Prosthetic joint	Not cultured	1200mg x 2 every 14d	HOIC	Cure	None	Prior TMP/SMX with improvement
60/M	Cellulitis, nonpurulent	Not cultured	1200mg x 2 every 10d	HOIC	Improvement	None	No prior therapy

Site of infusion: POIC, physician-owned infusion center; HOIC, hospital-owned infusion center; OP-HOU, outpatient hospital observation unit; ED, emergency department; IP, inpatient; HH, home health.
Drugs: ORI, oritavancin; VAN, vancomycin; TMP/SMX, trimethoprim-sulfamethoxazole; PTZ, piperacillin-tazobactam; DAL, dalbavancin; CFTX, ceftriaxone; A/S, ampicillin-sulbactam.

CONCLUSION

- Described are results from a real-world program which includes a multi-center, retrospective, observational study in patients that received > 1 dose of oritavancin for the treatment of gram-positive infections. This study confirms that oritavancin is an effective and well-tolerated long-acting lipoglycopeptide antibiotic used as single-dose treatment of ABSSSI, its approved indication, but also as multidose regimens for the treatment of complicated gram-positive infections.
- One retrospective case series of 17 patients evaluated the use of oritavancin as multidose treatment for a variety of complicated gram-positive infections.[7] While all patients received 1200 mg oritavancin as first dose, subsequent doses were lower (800 mg, 13 patients) when separated by 7 days or less. While Schulz et al[7] did not study serum concentrations, studies by both Johnson et al[5] and Foster et al[9] revealed that trough levels of oritavancin remained low and were similar to those reported in the literature from prior clinical trials with single-dose oritavancin.[11] In this report, all oritavancin doses were 1200 mg and was the practice at enrolling sites.
- Observational studies in real-world settings can serve as useful complements to randomized clinical trials (RCTs). Observational studies have the advantage of studying patients which are usually excluded from RCTs and acknowledging the use of antibiotics and their dosing reflecting actual use in practice.
- This study has important limitations. Data collected during this study include the retrospective, noncomparative, unblinded, and nonrandomized nature of the real-world evidence. Assessment of efficacy was based on a subjective assessment extracted from the medical record by the investigators. Missing data may have been encountered given the 30-day clinical assessment and 60-day safety evaluation windows. Although quality data checks were performed, the results of this study pertaining to patients receiving multiple-dose regimens of oritavancin should be verified in larger multicenter open-label cohort studies enrolling patients with complicated and microbiologically documented infections.

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