Poster # 443

THE CHROME STUDY, A REAL-WORLD EXPERIENTIAL REGISTRY ON THE USE OF ORITAVANCIN FOR TREATMENT OF GRAM-POSITIVE INFECTIONS

Mark Redell[1], Miguel Sierra-Hoffman[2], Maha Assi[3], Markian Bochan[4], David Chansolme[5], Anurag Gandhi[6], Kathleen Sheridan[7], Ivan Soosaipillai[8], Thomas Walsh[9], Jill Massey[1]

[1]Melinta Therapeutics, Morristown, New Jersey; [2]Infectious Disease and Pulmonary Consultants, Victoria, Texas; [3]IDC Clinical Research, Wichita, Kansas; [4]Infectious Diseases of Indiana, Indianapolis, Indiana; [5]Infectious Disease Consultants of Oklahoma City, Oklahoma City, Oklahoma; [6]Birmingham Infectious Disease and Infusion, Birmingham, Alabama; [7]University of Pittsburgh Physicians, Pittsburgh, Pennsylvania; [8]Infectious Disease Associates of North Central Florida, Ocala, Florida; [9]Allegheny-Singer Research Institute, Pittsburgh, Pennsylvania

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1-844-MED-MLNT
medinfo@melinta.com

INTRODUCTION & PURPOSE

- Oritavancin (ORI) is a bactericidal long-acting lipoglycopeptide antibiotic that is approved in the US for the treatment of adult patients with ABSSSI caused by designated Gram-positive pathogens including MRSA **[1]**.
- An interim analysis of a real-world registry, CHROME (Clinical and Historic Registry and Orbactiv Medical Evaluation), revealed clinical and microbiologic outcomes and safety of single-dose ORI 1200 mg similar to those observed in the phase 3 SOLO trials **[2]**.
- Prior success with ORI has stimulated clinical experimentation with multiple dose regimens for treatment of complicated Gram-positive infections. In this study, we sought to build upon prior reports of real-world use by describing the clinical characteristics and outcomes of a diverse cohort of patients with Gram-positive infections treated with at least one dose of ORI.

METHODS

- Patients who received at least one dose of ORI were eligible for inclusion. Sites enrolled patients between Oct 2014 to Oct 2017.
- To be included, patients had to (1) be treated with ORI for a suspected or confirmed Gram-positive infection, and (2) have received the last dose of ORI at least 60 days prior to data entry.
- Safety definitions were established prior to patient enrollment. Safety data were collected up to 60 days following the last dose of ORI. Adverse events with a reasonable possibility of a causal relationship to ORI were reported.
- Outcomes considered only Gram-positive pathogens related to the primary infection process. Clinical and microbiologic categories of efficacy were assessed between end of infusion of last dose plus 30 days. Clinical categories of efficacy were defined as: clinical cure (clinical signs and symptoms resolved), clinical improvement (partial resolution of clinical signs and symptoms), or clinical failure (inadequate resolution, or new or worsening clinical signs and symptoms). Microbiological response was defined as either microbiologic eradication (documentation of a negative bacterial culture from the same site as the initial positive baseline culture) or microbiologic persistence (bacterial growth of the same organism from the same site as the initial positive baseline culture). Presumed eradication was based on favorable clinical outcomes.

RESULTS

- Data for 440 patients were collected from 26 geographically dispersed U.S. healthcare sites. Patient demographics and baseline characteristics are presented in **Table 1**.
- Infection types are listed in **Table 2.** Skin and soft tissue infections (SSTIs) accounted for the majority of infections (91.1%). Seven patients received ORI for bacteremia (MRSA, 2; MSSA, 1; *S. epidermidis*, 2; unknown, 2).
- In the 30 days prior to the first dose of ORI, 71.4% of patients received at least one non-ORI systemic antimicrobial **(Table 2).** In patients receiving > 1 dose of ORI, only 1 patient received a systemic antibiotic as concomitant therapy. After the last dose of ORI, 44 patients received additional antibiotics due to treatment failure (31 of 52 patients, 59.6%), AEs to ORI (2 patients), and prevention of recurrence (11 patients, 21.1%).
- Infection type was examined in **Table 3** according to administration of ORI as single doses (408 patients, 92.7%) and multiple doses (32 patients, 7.3%). Multiple dose administration of ORI was defined as interruption between doses by 14 days or less.
- Clinical outcomes are provided in **Table 4** (438 evaluable patients) and compare single dose and multiple dose ORI overall and in bone and joint infections. Thirty-two patients in the multiple-dose ORI cohort were treated with 2 to 10 doses. Clinical failures in 2 patients included: 1 patient requiring amputation due to MRSA-related osteomyelitis and 1 patient with a traumatic wound with a positive culture for *Corynebacterium striatum* which persisted following 3 doses of ORI infused every 14 days. Eighteen patients with osteomyelitis were treated with ORI – 8 with multiple doses and 10 with a single dose, the latter for completion of therapy for osteomyelitis. Seven patients with bacteremias, all treated with single dose ORI, were clinical cures.
- The evaluable safety cohort is discussed in **Table 5**. The most common event was pruritis (3.2% [14/440]). There was one patient who experienced 3 serious AEs (nausea, vomiting and asthenia). ORI was discontinued in 6 patients. These events included: 1) infusion site reaction; 2) pruritis, urticaria and headache; 3) urticaria and pruritis; 4) headache and throat tightness; 5) non-specified infusion-related reaction; and 6) back pain and flushing. The patient who experienced an infusion site reaction was observed in the ER and discharged within a few hours. In the other five patients, AEs resolved spontaneously within 90 minutes after discontinuation; all were discharged home. All AEs were manifested between 25 minutes and 2 hours from initiation of a 3-hour infusion. There were no deaths during the observation period.

TABLE 1. Baseline Characteristics (n=440)

Characteristic	Value
Age (yrs)	
Mean (SD)	57.8 (16.4)
Range	18 - 98
≥ 65 yrs	37.0
Male (%)	53.2
Race, white (%)	93.0
BMI (kg/m2)	
Mean (SD)	32.8 (9.0)
Range	14 - 65
SIRS, at presentation (%) [a]	8.3
WBC > 12,000 cells/mm^3 (%)	15.6
Co-morbidities, %	
Hypertension	53.4
Diabetes mellitus	39.5
Diabetic neuropathy	12.3
Diabetic foot infection	8.6
Hyperlipidemia	31.4
Peripheral vascular disease/lymphedema	17.3
Coronary artery disease	14.3
COPD/asthma	13.2
Chronic kidney disease	9.3
Neoplastic disease	7.0

[a] Systemic inflammatory response syndrome (SIRS) is defined as two of the following: temperature >38° C, pulse >90 beats per minute, respiratory rate >20 breaths per minute, white blood cell (WBC) count >12,000 mm^3 or <4,000 mm^3 or >10% bandemia.

TABLE 2. Infection, Microbiology, Prior Antibiotic Use

Infection Classification	No. (%)
Skin and soft tissue	401 (91.1)
Cellulitis	270 (67.3)
Wound	67 (16.7)
Abscess	64 (16.0)
Bacteremia	7 (1.6)
Primary	5
Secondary to SSTI	2
Other	32 (7.3)
Osteomyelitis	18
Prosthetic joint infection	3
Septic arthritis/synovitis	4
Catheter exit site	1
Infected bursa	3
Maxillary sinus infection	1
Hardware, posterior lumbar tissue	1
Lymphadenitis	1
Positive cultures	146/440 (33.2)
Staphylococcus aureus	108 (74.0)
MSSA	44 (40.7)
MRSA	64 (59.3)
Prior antibiotic therapy [a]	314/440 (71.4)
Cephalosporins	154 (48.9)
Vancomycin	153 (48.7)
Trimethoprim/sulfamethoxazole	67 (21.3)
Clindamycin	59 (18.8)

[a] In CHROME, receipt of at least one systemic antibiotic (non-ORI) related to the index infection within 30 days prior to the first dose of ORI.

TABLE 3. Dosing By Infection Category [a]

Infection Category and Dosing	No. (% of 440)
Skin and soft tissue	401 (91.1)
Single dose	380 (94.8)
Multiple dose	21 (5.2)
Bacteremia	7 (1.6)
Single	7 (1.6)
Multiple	0
Other	32 (7.3)
Osteomyelitis	18 (4.1)
Single dose	10
Multiple dose	8
Septic arthritis, synovitis	4 (0.91)
Single dose	2
Multiple dose	2
Prosthetic joint infection	3 (0.68)
Single dose	2
Multiple dose	1
Other [b]	7 (1.6)
Single dose	7
Multiple dose	0

[a] Multiple-dose ORI includes treatment courses in which dose were interrupted by no more than 14 days. For skin and soft tissue, multiple doses include: cellulitis (n=10), wound (n=8), abscess (n=2), burn (n=1)
[b] Includes: catheter exit site (1); infected bursa (3); maxillary sinus infection (1); hardware, posterior lumbar tissue (1); and, lymphadenitis (1).

TABLE 4. Clinical and Microbiologic Outcomes (n=438)

Outcome	Single Dose (n/N)	Multiple Doses (n/N)	Overall (n/N)
Clinical success (all)	87.7% (356/406)	93.8% (30/32)	88.1% (386/438)
Clinical success			
Bone & joint (includes osteo)	78.6% (11/14)	90.9% (10/11)	84.0% (21/25)
Joint	50.0% (2/4)	100% (3/3)	71.4% (5/7)
Osteomyelitis	90.0% (9/10)	87.5% (7/8)	88.9% (16/18)
Clinical failure	12.3% (50/406)	6.2% (2/32)	11.9% (52/438)
Microbiological [a] eradication	28	1	78.4% (29/37)
Microbiological persistence [a]	7	1	21.6% (8/37)

[a] One patient in the multiple dose group (3 doses within 14 days apart) revealed microbiologic persistence while one patient in the multiple-dose group (2 doses 14 days apart) revealed microbiologic eradication.

TABLE 5. Treatment Emergent Adverse Events (n=440) [a]

Adverse Event (%, [n/N]))	Single Dose (n=408)	Multiple Dose (n= 32)	All Patients (n=440)
Any drug-related adverse event	6.6 (27/408)	6.3 (2/32)	6.6 (29/440)
Serious drug-related adverse event	0.2 (1/408)	0 (0/32)	0.2 (1/440)
Discontinuation due to any adverse event	1.2 (5/408)	3.1 (1/32)	1.4 (6/440)
Incidence of selected adverse event (%, [n/N])			
Hypersensitivity			1.1 (5/440)
Diarrhea			0.7 (3/440)
Vomiting			0.7 (3/440)
Clostridioides difficile-associated diarrhea [b]			0.2 (1/440)

[a] Adverse events with a reasonable possibility of a causal relationship to ORI were reported.
[b] The single patient with *Clostridioides difficile*-associated diarrhea was identified in a single-dose patient.

CONCLUSIONS

- The clinical efficacy of ORI has been well established in clinical trials in ABSSSI. However, there is a plethora of patient cases and case series describing the real-world use of ORI in multiple-dose regimens for the treatment of bone and joint infections, pneumonia, bacteremia, and complicated surgical site infections **[3-9]**.
- Described in this registry of 440 patients are results from a real-world program CHROME which includes a multi-center, retrospective, observational approach to study of patients that received at least one dose of ORI for the treatment of Gram-positive infections. This study confirms that ORI is an effective and well-tolerated long-acting lipoglycopeptide antibiotic used as single-dose treatment of ABSSSI, its approved indication, but also as multiple-dose regimens for the treatment of complicated Gram-positive infections, including osteomyelitis. In this report, all ORI doses were 1200 mg as was the practice at enrolling sites.
- This study has important limitations. Data collected during this study was retrospective, noncomparative, unblinded, and nonrandomized. Assessment of efficacy was based on a subjective assessment extracted from the medical record by Investigators. Missing data may have been encountered. Additional real-world experience of patients receiving multiple-dose regimens of ORI should be studied enrolling patients with complicated infections which may identify the optimal effective and safe dose and dosing interval.

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