Efficacy and Safety of Omadacycline in Chronic Kidney Disease (CKD) Patients With Acute Bacterial Skin and Skin Structure Infections (ABSSSI): A Subgroup Analysis From the OASIS Trial

Poster 1834

Thomas M. File Jr, MD, MSc[1]; Nancy Cure-Bolt, MD[2]; Surya Chitra, PhD, MBA[2]; Evan Tzanis, BA[2]; Paul McGovern, MD[2]

[1]Infectious Disease Division, Summa Health, Akron, OH, USA; [2]Paratek Pharmaceuticals, King of Prussia, PA, USA

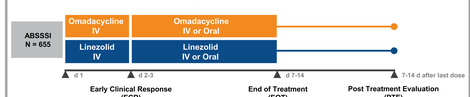
BACKGROUND

- The incidence and severity of acute bacterial skin and skin structure infections (ABSSSI) have increased in recent years[1,2]
  - Nearly 5 million hospital admissions from 2005 to 2011 were due to a primary diagnosis of skin and skin structure infections
  - ABSSSI include cellulitis, erysipelas, wound infections, and major cutaneous abscesses
- Omadacycline (OMC), a first-in-class aminomethylcycline antibiotic, is a semisynthetic derivative of the tetracyclines that exhibits activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical bacteria[3-7]
- Oral OMC is predominantly eliminated in the feces, but an appreciable portion of the bioavailable dose (~27%) is eliminated, mainly as unmetabolized OMC, in the urine[8]
- In the **O**madacycline in **A**cute **S**kin and Skin Structure **I**nfections **S**tudy (OASIS-1, NCT02378480), intravenous to oral OMC demonstrated non-inferiority to intravenous to oral linezolid (LZD) for the treatment of ABSSSI with comparable safety in the general population.[9] In the OASIS-2 study (NCT02877927), oral-only administration of OMC demonstrated non-inferiority to oral LZD for the treatment of ABSSSI with comparable safety in the general population[10]
  - A phase 1 study in patients with ESRD and on hemodialysis suggests that no change in dosing is necessary when OMC is given before or after dialysis[11]
- Reports state that ~10% of patients hospitalized for ABSSSI have moderate to severe renal disease[1]
  - Renal impairment and hemodialysis may lead to alteration in antibiotic PK, necessitating dosage adjustment[12]
  - Examples of such antibiotics (depending on varying degrees of renal impairment) include vancomycin, telavancin, ceftaroline, levofloxacin, cefpodoxime, daptomycin, dalbavancin, trimethoprim-sulfamethoxazole, clarithromycin, cefazolin, cephalexin, oxacillin, and amoxicillin
- The goal of this work was to determine if renal impairment has any effect on the efficacy or safety of OMC in patients from OASIS-1

METHODS

- OASIS-1 was a randomized (1:1), double-blind, phase 3 study comparing OMC and LZD for the treatment of adults with ABSSSI[9] (**Figure 1**)
  - Patients randomized to OMC treatment were administered OMC 100 mg intravenously (IV) every 12 hours (q12h) for 2 doses, followed by 100 mg IV OMC every 24 hours (q24h), for a minimum of 3 days of IV OMC. Patients could then transition to 300 mg OMC administered orally q24h for a total treatment duration of 7 to 14 days
  - Patients randomized to LZD treatment were administered LZD 600 mg IV q12h. After a minimum of 3 days of IV therapy, patients could transition to oral LZD, with 600 mg administered every 12 hours, with a total treatment duration of 7 to 14 days

Figure 1. OASIS-1 study design.



- Patients from OASIS-1 were classified on the basis of renal function (**Figure 2**)
  - Stage 0/1 chronic kidney disease (CKD-0/1): Glomerular filtration rate ≥ 90 mL/min
  - Stage 2/3 chronic kidney disease (CKD-2/3): Glomerular filtration rate = 30-89 mL/min

METHODS

- Study endpoints were
  - Early clinical response (ECR): Survival with ≥20% reduction in lesion size at 48 to 72 hours after first dose of OMC or LZD
  - Clinical success at post treatment evaluation (PTE; assessed at 7 to 14 days after the last dose of OMC or LZD): Survival with resolution of signs and symptoms of the infection such that further antibacterial therapy is not needed
  - Patients whose clinical response to OMC or LZD could not be adequately inferred due to withdrawal of consent, loss to follow-up, or other specified reason were considered indeterminate
- Any systemic or topical antibacterial agent with a spectrum that is active against the potential infecting pathogen(s) responsible for the ABSSSI under study was prohibited, except in cases of clinical failure
- Bacterial pathogens were identified from a biopsy of the involved tissue at baseline (Day –1 or 1). For patients with cellulitis/erysipelas, if no infectious material had been obtained or no pathogen identified, a Day 2 or 3 sample was used as baseline
- Any planned surgical treatments were to be performed within 24 hours and no later than 48 hours after the first dose of OMC or LZD
- Safety was assessed based on adverse events, vital signs, electrocardiograms, and standard clinical laboratory tests
- Populations for analysis
  - Modified intent-to-treat (mITT): All randomized patients without a baseline sole Gram-negative ABSSSI pathogen
  - Clinically evaluable (CE): Patients in the mITT population who received at least 1 dose of OMC or LZD, in whom the overall clinical response was not indeterminate at PTE and the PTE visit occurred 7 to 14 days after last dose of OMC or LZD
  - Safety: All randomized patients who received any dose of OMC or LZD
  - micro-mITT: All patients in the mITT population who had at least 1 Gram-positive causative bacterial pathogen identified at baseline

RESULTS

Figure 2. Subgroup breakdown.

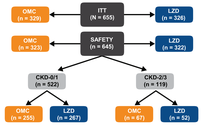
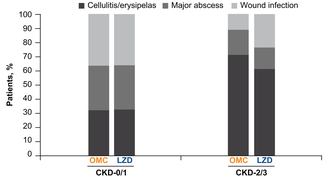


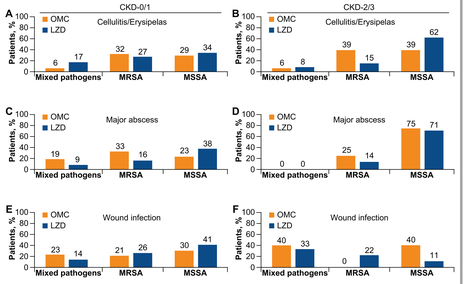
Figure 3. Baseline infections in CKD-0/1 and CKD-2/3 subgroups (mITT population).



- Baseline infections were generally similar between OMC- and LZD-treated patients (**Figure 3**)
- Cellulitis/erysipelas was more frequent in patients with CKD-2/3

RESULTS

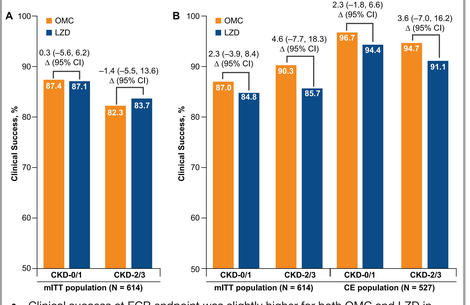
Figure 4. Select baseline pathogens in (A) CKD-0/1 and (B) CKD-2/3 (micro-mITT population).



Mixed pathogens includes all patients with ≥ 2 pathogens identified.
The percentage is based on the number of patients with the infection type in each treatment arm.

- Overall, baseline pathogens were generally similar across most subgroups and infection types
  - *Staphylococcus aureus* was the most common pathogen, and MRSA was present in up to 39% of patients (**Figure 4**)
  - In wound infections, CKD-2/3 patients had a higher proportion of mixed pathogens (**Figure 4**)

Figure 5. Clinical success at (A) ECR endpoint and (B) PTE.



- Clinical success at ECR endpoint was slightly higher for both OMC and LZD in patients with CKD-0/1 compared to patients with CKD-2/3 (**Figure 5A**)
- Clinical success at PTE was numerically higher for OMC compared to LZD in both the CKD-0/1 and CKD-2/3 subgroups for the mITT population and the CE population (**Figure 5B**)
- Differences in clinical success rates between OMC- and LZD-treated patients were not statistically significant in either CKD subgroup

RESULTS

Table 1. Overview of Treatment-Emergent Adverse Events

	CKD-0/1		CKD-2/3	
	OMC N = 255	LZD N = 267	OMC N = 67	LZD N = 52
Subjects with at least 1 TEAE, n (%)	129 (50.59)	130 (48.69)	26 (38.81)	16 (30.77)
Drug-related TEAEs, n (%)	33 (12.94)	39 (14.61)	6 (8.96)	3 (5.77)
Severe TEAEs, n (%)	3 (1.18)	4 (1.50)	0	2 (3.85)
Serious TEAEs, n (%)	3 (1.18)	2 (0.75)	0	2 (3.85)
Drug-related serious TEAEs, n (%)	0	0	0	0
TEAEs leading to discontinuation, n (%)	5 (1.96)	4 (1.50)	0	0
Serious TEAEs leading to death, n (%)	0	1 (0.37)	0	1 (1.92)

TEAE, treatment-emergent adverse event.

- Overall TEAEs and drug-related TEAEs are comparable among OMC- and LZD-treated patients in both CKD subgroups. There were no drug-related serious TEAEs observed for OMC or LZD treatment (**Table 1**)
  - In patients with CKD-2/3, fewer patients experienced at least 1 TEAE. This was primarily due to differences in nausea, diarrhea, and infusion site extravasation (see **Table 2**, below, for further details)

Table 2. Frequency of Gastrointestinal, Liver Chemistry, and Infusion Site Extravasation Treatment-Emergent Adverse Events

	CKD-0/1		CKD-2/3	
	OMC N = 255	LZD N = 267	OMC N = 67	LZD N = 52
Gastrointestinal TEAEs, n (%)				
Nausea	10 (3.92)	14 (5.24)	3 (4.48)	1 (1.92)
Diarrhea	4 (1.57)	8 (3.00)	2 (2.99)	0
Vomiting	2 (0.78)	2 (0.75)	0	0
Liver Chemistry TEAEs, n (%)				
ALT increased	6 (2.35)	12 (4.49)	1 (1.49)	2 (3.85)
AST increased	3 (1.18)	1 (0.37)	0	0
Infusion site extravasation, n (%)	15 (5.88)	7 (2.62)	2 (2.99)	1 (1.92)

ALT, alanine aminotransferase; AST, aspartate aminotransferase; TEAE, treatment-emergent adverse event.

RESULTS

- Overall, gastrointestinal TEAEs were moderate and generally similar between OMC and LZD treatment across both subgroups (**Table 2**)
- There were minor variations in liver chemistry TEAEs between regimens across subgroups
- 79% of patients in each treatment group had ABSSSI considered related to IV drug use. All infusion site extravasation events were mild and typically due to difficulty in finding reliable venous access sites.

CONCLUSIONS

- IV to once-daily oral omadacycline was effective and well tolerated for treating ABSSSI in patients with CKD-0/1 and CKD-2/3
  - No differences in efficacy at ECR endpoint or PTE were observed between omadacycline and linezolid treatment in either subgroup
  - Overall, TEAEs were generally comparable between omadacycline and linezolid treatment
- The safety and efficacy of omadacycline in patients with CKD-0/1 and CKD-2/3 are similar
- Taken together with data from a phase 1 renal impairment study,[11] this subgroup analysis supports the use of omadacycline in patients with renal impairment and ABSSSI

REFERENCES

1. Kaye KS, et al. *PLoS One*. 2015;10:e0143276.
2. US FDA. Guidance for Industry. Acute Bacterial Skin and Skin Structure Infections: Developing Drugs for Treatment. 2013.
3. Villano S, et al. *Future Microbiol*. 2016;11:1421-1434.
4. Honeyman L, et al. *Antimicrob Agents Chemother*. 2015;59:7044-7053.
5. Draper MP, et al. *Antimicrob Agents Chemother*. 2014;58:1279-1283.
6. Tanaka SK, et al. *Bioorg Med Chem*. 2016;24:6409-6419.
7. Macone AB, et al. *Antimicrob Agents Chemother*. 2014;58:1127-1135.
8. Flarakos J, et al. *Xenobiotica*. 2017;47(8):682-696.
9. O'Riordan WA, et al. ECCMID 2017. Abstract 630.
10. Paratek Pharmaceuticals [press release]. Boston, MA; July 17, 2017.
11. Berg J, et al. ASM 2017. Abstract 3397.
12. Eyler RF, Mueller BA. *Adv Chronic Kidney Dis*. 2010;17:392-403.

FUNDING AND DISCLOSURES

This work was funded by Paratek Pharmaceuticals, Inc.

ACKNOWLEDGMENT

Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by Healthcare Consultancy Group.

Presented at: IDWeek 2017; October 4-8, 2017; San Diego, CA.