Clinical Outcomes of Patients With Secondary Bacteremia in the Omadacycline Phase 3 Acute Bacterial Skin and Skin Structure Infections and Community-Acquired Bacterial Pneumonia Studies

Poster 110

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BACKGROUND

- The aminomethylcycline omadacycline (OMC) is approved in the United States for the treatment of adults with acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP)[1]
  - Aminomethylcyclines are semisynthetic antibiotics related to the tetracyclines[2,3]
  - Modifications in the chemical structure of OMC allow it to overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection
- OMC showed non-inferiority to linezolid (LZD) in two ABSSSI studies (**O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy [OASIS]-1 and 2),[4,5] and to moxifloxacin (MOX) in a CABP study (**O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity [OPTIC])[6]
- Low serum concentrations of tetracycline antibiotics may raise concerns about their efficacy in patients with secondary bacteremia, especially in comorbid patients and in those with higher acuity of illness

Objectives of Analysis

- To evaluate clinical outcomes in patients with secondary bacteremia identified in the OASIS-1 and 2 (ABSSSI) and OPTIC (CABP) studies, and provide descriptive assessment of demographic and baseline characteristics

METHODS

Phase 3 Study Designs

- All studies involved 7-14 days' therapy with test article
- ABSSSI: OASIS-1, intravenous (IV) to oral OMC versus IV to oral LZD;[4] OASIS-2, once-daily oral OMC versus twice-daily oral LZD[5]
- CABP: OPTIC, IV to oral OMC versus IV to oral MOX[6]

Blood Cultures

- Baseline blood cultures collected from all patients enrolled in each study within 24 h of first dose of study drug
  - Bacterial isolates that grew in the site's local microbiology laboratory were shipped to a central microbiology laboratory for confirmation of identification (genus, species) and susceptibility testing
  - If blood cultures were positive for pathogen growth, they were to be repeated until negative

Primary Efficacy Endpoints

- Early clinical response (ECR) was based on lesion measurements determined programmatically per US Food and Drug Administration (FDA) guidance, at 48-72 h (ABSSSI) or 72-120 h (CABP) based on signs and symptoms after first dose of study drug; ECR was defined as follows:
  - ABSSSI studies: survival with a ≥20% reduction in lesion size compared to screening measurements without receiving any rescue antibacterial therapy
  - CABP study: survival with investigator-assessed improvement in at least two of four symptoms (cough, sputum production, pleuritic chest pain, dyspnea), without deterioration these symptoms, and without any use of rescue antibacterial therapy
- Investigator's assessment of clinical response at post treatment evaluation (PTE) 7-14 days (ABSSSI) or 5-10 days (CABP) after last dose of study drug
  - Clinical success defined as survival with resolution of infection to the extent that further antibiotic treatment was not necessary, and without the use of rescue antibacterial therapy

RESULTS

Demographic and Baseline Characteristics

- ABSSSI randomized patients without a sole Gram-negative pathogen at baseline: N=1,347 (OMC, n=676; LZD, n=671)
- CABP randomized patients: N=774 (OMC n=386; MOX n=388)
- Secondary bacteremia was confirmed in 63/2,121 patients (3%) across the three studies
  - Demographic characteristics were similar between treatment groups (**Table 1**); there were more male patients in the LZD group than in the OMC group, in ABSSSI studies

Table 1. Demographic and Baseline Characteristics of Patients With Secondary Bacteremia Included in Phase 3 Studies of Omadacycline

	CABP (OPTIC)		ABSSSI (OASIS-1, -2)	
Characteristic	OMC N=15	MOX N=18	OMC N=13	LZD N=17
Median age (range), years	58.0 (38-86)	60.0 (32-83)	45 (26-84)	54 (23-80)
Male, n (%)	8 (53.3)	10 (55.6)	3 (23.1)	11 (64.7)
Race, n (%)				
Caucasian	14 (93.3)	16 (88.9)	13 (100)	15 (88.2)
Median body mass index kg/m^2 (range)	28 (22-41)	27 (13-33)	24 (20-33)	28 (22-55)

ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; LZD = linezolid; MOX = moxifloxacin; OASIS = **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy; OMC = omadacycline

Microbiologic Findings and Treatment Duration

- *Streptococcus pneumoniae* was the most frequent cause of secondary bacteremia in CABP (**Table 2**) (N=33; OMC, 11/15; MOX, 11/18)
  - OMC minimum inhibitory concentration $(MIC)_{90}$ = 0.06 ug/mL
  - Median treatment duration:
    - Patients with secondary bacteremia: 11 days (OMC) and 14 days (MOX)
    - All patients (safety population): 10 days (OMC) and 10 days (MOX)

Table 2. Baseline Pathogens Identified From Blood Specimens in CABP Patients in OPTIC

Pathogen	Omadacycline N=15 n (%)	Moxifloxacin N=18 n (%)
Gram-positive bacteria (aerobes)	12 (80.0)	13 (72.2)
Streptococcus pneumoniae	11 (73.3)	11 (61.1)
Streptococcus mitis	1 (6.7)	2 (11.1)
Staphylococcus aureus (MSSA)	1 (6.7)	0
Gram-negative bacteria (aerobes)	3 (20.0)	5 (27.8)
Acinetobacter baumannii	0	1 (5.6)
Acinetobacter lwoffii	1 (6.7)	0
Escherichia coli	0	4 (22.2)
Haemophilus influenzae	1 (6.7)	0
Klebsiella pneumoniae	1 (6.7)	0

CABP = community-acquired bacterial pneumonia; MSSA = methicillin-susceptible *Staphylococcus aureus*; OPTIC = **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity study
Percentages are based on the number of patients with bacteremia (positive blood culture), with the specified pathogen

RESULTS

- *Staphylococcus aureus* was the most frequent cause of secondary bacteremia in ABSSSI (**Table 3**) (N=30: OMC, 7/13; LZD, 9/17)
  - OMC minimum inhibitory concentration $(MIC)_{90}$ = 0.50 ug/mL
  - Median treatment duration:
    - Patients with secondary bacteremia: 9 days (OMC) and 10 days (LZD)
    - All treated patients (safety population): 9 days (OMC) and 9 days (LZD)

Table 3. Baseline Pathogens Identified from Blood Specimens in ABSSSI Patients in OASIS-1 and -2

Pathogen	Omadacycline N=13 n (%)	Linezolid N=17 n (%)
Gram-positive bacteria (aerobes)	13 (100.0)	16 (94.1)
Staphylococcus aureus	7 (53.8)	9 (52.9)
MRSA	3 (23.1)	3 (17.6)
MSSA	4 (30.8)	6 (35.3)
Streptococcus anginosus group	1 (7.7)	1 (5.9)
Streptococcus anginosus	1 (7.7)	0
Streptococcus intermedius	0	1 (5.9)
Enterococcus faecalis (VSE)	0	1 (5.9)
β-hemolytic streptococci	3 (23.1)	3 (17.6)
Group A or *Streptococcus pyogenes*	2 (15.4)	3 (17.6)
Group G or *Streptococcus dysgalactiae*	1 (7.7)	0
Granulicatella adiacens	0	1 (5.9)
Rothia dentocariosa	0	1 (5.9)
Streptococcus sanguinis	1 (7.7)	0
Viridans streptococci	1 (7.7)	1 (5.9)
Gram-negative bacteria (aerobes)	0	1 (5.9)
Moraxella lacunata	0	1 (5.9)

MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; OASIS = **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy; VSE = vancomycin-sensitive enterococci
Percentages are based on the number of patients with bacteremia (positive blood culture), with the specified pathogen

Efficacy Findings

- Clinical success rates in patients with secondary bacteremia were numerically lower in the OMC groups at both time points (~20% lower at ECR and ~10% lower at PTE in both indications) (**Tables 4** and **5**), however, small sample sizes in both treatment groups limit interpretation of these differences
  - Reasons for failure were often protocol deviations (e.g. use of rescue antibacterial therapy when investigator became aware of baseline blood culture results)

RESULTS

Table 4. Clinical Outcomes at ECR and PTE Among CABP Patients With Secondary Bacteremia, OPTIC Study

Clinical Outcome	OMC N=15 n (%)	MOX N=18 n (%)
ECR		
Clinical success	10 (66.7)	16 (88.9)
Clinical failure	2 (13.3)	2 (11.1)
Indeterminate	3 (20.0)	0
PTE		
Clinical success	11 (73.3)	15 (83.3)
Clinical failure	3 (20.0)	3 (16.7)
Indeterminate	1 (6.7)	0

CABP = community-acquired bacterial pneumonia; ECR = early clinical response; MOX = moxifloxacin; OPTIC = **O**madacycline for **P**neumonia **T**reatment **I**n the **C**ommunity study; PTE = post treatment evaluation
Percentages calculated from number of patients with a given outcome divided by number of patients with or without bacteremia

CABP Patients with Secondary Bacteremia and Clinical Failure or Indeterminate Outcome at PTE

- OMC 1: *Klebsiella pneumoniae* (MIC of 2 ug/mL) in blood, no follow-up cultures, received non-study antibiotic from Day 1, clinical failure at PTE
- OMC 2: *S. pneumoniae* (MIC of 0.12 ug/mL) in blood and *Haemophilus influenzae* in sputum, no follow-up cultures, died on Day 2 due to septic shock, clinical failure at PTE
- OMC 3: *S. pneumoniae* (MIC of 0.03 ug/mL) in blood and sputum, no follow-up cultures, received non-study antibiotic from Day 3, clinical failure at PTE
- OMC 4: Methicillin-susceptible *S. aureus* (MSSA) (MIC of 0.12 ug/mL) in blood at screening and repeat cultures on Days 4 and 6, no further follow-up cultures after Day 6, clinical success at end of treatment on Day 15, indeterminate clinical response at PTE (missed visit)
- MOX 1: *Escherichia coli* (MIC of 0.12 ug/mL) in blood at screening and repeat cultures on Days 2 and 3, no further follow-up cultures after Day 3, died on Day 9 due to cardiac failure, clinical failure at PTE
- MOX 2: *E. coli* (MIC of 0.25 ug/mL) in blood, no follow-up cultures, received non-study antibiotics for a non-CABP infection starting on Day 6, clinical failure at PTE
- MOX 3: *E. coli* (MIC of 0.06 ug/mL) in blood and positive serology for *Mycoplasma pneumoniae*, follow-up blood culture Day 10 was negative. Methicillin-resistant *S. aureus* was identified in sputum on Day 10 (new infection), received non-study antibiotic starting on Day 10, clinical failure at PTE

Table 5. Clinical Outcomes at ECR and PTE Among ABSSSI Patients With Secondary Bacteremia, OASIS-1 and -2 Studies

Clinical Outcome	OMC N=13 n (%)	LZD N=17 n (%)
ECR		
Clinical success	8 (61.5)	14 (82.4)
Clinical failure	3 (23.1)	1 (5.9)
Indeterminate	2 (15.4)	2 (11.8)
PTE		
Clinical success	10 (76.9)	14 (82.4)
Clinical failure	3 (23.1)	2 (11.8)
Indeterminate	0	1 (5.9)

ABSSSI = acute bacterial skin and skin structure infection; ECR = early clinical response; LZD = linezolid; mITT = modified intent-to-treat; OASIS = **O**madacycline in **A**cute **S**kin and skin structure **I**nfections **S**tudy; OMC = omadacycline; PTE = post treatment evaluation
Percentages calculated from number of patients with a given outcome divided by number of patients with or without bacteremia

RESULTS

ABSSSI Patients with Secondary Bacteremia and Clinical Failure or Indeterminate Outcome at PTE

- OMC 1: MSSA (MIC of 0.25 ug/mL) in blood, follow-up blood culture on Day 2 was positive, received non-study antibiotics starting on Day 3, clinical failure at PTE
- OMC 2: Viridans group streptococci (MIC 0.06 ug/mL) in blood, follow-up blood culture on Day 2 was negative, received non-study antibiotics starting on Day 8 for treatment of the primary ABSSSI
- OMC 3: MSSA (MIC of 0.25 ug/mL) in blood and lesion, and *Streptococcus agalactiae* (Group B) in lesion at screening, follow-up blood culture on Day 2 was negative, received non-study antibiotics starting on Day 3, clinical failure at PTE
- LZD 1: MSSA (MIC of 2 ug/mL) in blood and lesion, and *Proteus mirabilis* in lesion at screening, follow-up blood culture on Day 2 was negative, received non-study antibiotics starting on Day 4, clinical failure at PTE
- LZD 2: MSSA (MIC of 2 ug/mL) in blood and lesion, follow-up blood culture on Day 2 was negative, received non-study antibiotics starting on Day 4, clinical failure at PTE
- LZD 3: *Streptococcus pyogenes* (no susceptibility results available) in blood, no follow-up cultures, patient was lost to follow-up after receiving one dose of study drug, indeterminate clinical response at PTE

CONCLUSIONS

- No case of clinical failure was directly due to persistent bacteremia
- Indeterminate outcomes were due to missing data; failures were in most cases due to introduction of rescue antibacterial therapy in reaction to positive baseline blood cultures
- Although these findings are limited by the small sample size, clinical success rates at PTE were similar between omadacycline and comparators, in study participants with secondary bacteremia
- These findings provide preliminary reassurance for use of omadacycline in patients with secondary bacteremia

REFERENCES

1. Omadacycline (NUZYRA®) prescribing information, https://www.nuzyra.com/nuzyra-pi.pdf.
2. Villano S, et al. Future Microbiol. 2016;11:1421-1434.
3. Honeyman L, et al. Antimicrob Agents Chemother. 2015;59:7044-7053.
4. O'Riordan W, et al. N Engl J Med. 2019;380:528-538.
5. O'Riordan W, et al. Lancet Infect Dis. 2019 Aug 29 [Epub ahead of print].
6. Stets R, et al. N Engl J Med. 2019;380:517-527.

FUNDING AND DISCLOSURES

George Sakoulas, Anita F. Das, and Paul B. Eckburg have received consulting fees from Paratek Pharmaceuticals, Inc. Amy Manley and Bob Noble are employees of Paratek Pharmaceuticals, Inc. Lynne Garrity-Ryan, Evan Tzanis, Maria Curran and Paul C. McGovern were employees of Paratek Pharmaceuticals, Inc. at the time of the reported research. This study was sponsored by Paratek Pharmaceuticals, Inc. Medical editorial assistance, funded by Paratek Pharmaceuticals, Inc., was provided by Innovative Strategic Communications.

ACKNOWLEDGMENTS

The authors thank the patients and investigators involved in the OPTIC, OASIS-1, and OASIS-2 studies.

Presented at: IDWeek; October 2-6, 2019; Washington, DC