Analysis of the Microbiological Data From the Omadacycline (OMC) Phase 3 Community-Acquired Bacterial Pneumonia (CABP) Trial: The OPTIC Study

Poster 1875

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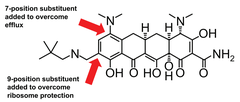
BACKGROUND

- Omadacycline (OMC) is the first aminomethylcycline in late-stage clinical development. Aminomethylcyclines are semisynthetic antibiotics related to the tetracyclines[1,2]
  - Modifications in the chemical structure of OMC allow it to overcome the 2 main mechanisms of tetracycline resistance, efflux pumps and ribosomal protection[3,4]

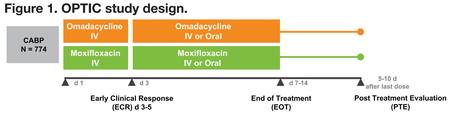


  - OMC demonstrates potent, broad-spectrum *in vitro* activity against common Gram-positive aerobes (including methicillin- and penicillin-resistant strains), Gram-negative aerobes, anaerobes, and atypical bacterial pathogens[4,5]
- OMC has completed phase 3 clinical development as an intravenous (IV) to once-daily oral monotherapy for community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) and as oral only monotherapy for ABSSSI[6-8]

METHODS

Study Design and Treatment

Figure 1. OPTIC study design.



- OPTIC was a randomized (1:1), double-blind, global study comparing OMC and moxifloxacin (MOX) for the treatment of adults with CABP (PORT Risk Class II [≤ 15% total enrollment], III, or IV; **Figure 1**)
- Treatment
  - OMC was administered at 100 mg IV q12h×2 doses, followed by 100 mg IV q24h, with the option to transition to oral (PO) OMC 300 mg q24h after a minimum of 3 days of IV treatment
  - MOX was administered at 400 mg IV q24h with the option to transition to 400 mg PO q24h after a minimum of days of IV treatment
  - Total treatment duration was 7 to 14 days

Analysis Population

- Clinical outcomes were analyzed in the microbiologic intent-to-treat (microITT) population defined as all patients in the intent-to-treat population who had at least 1 causative bacterial pathogen identified at baseline from culture of a respiratory or blood specimen, or from a non-culture method
- Clinical success at PTE was defined as resolution of signs and symptoms of infection such that further antibiotic treatment was not needed

Collection of Isolates

- Culture of a respiratory pathogen from a blood sample or an adequate quality expectorated or induced sputum or other respiratory specimen reflecting fluid from the lower respiratory tract was collected at the screening visit
- An adequate quality sputum specimen was defined as having the following 2 findings as reported by the local laboratory:
  - Less than 10 squamous epithelial cells/low power field (lpf; ie, 100×)
  - Greater than 25 polymorphonuclear cells/lpf (ie, 100×)
- Additionally, *Legionella pneumophila* or *Streptococcus pneumoniae* antigen detection in the screening urine sample and/or appropriate serology titers for *L. pneumophila*, *Mycoplasma pneumoniae*, or *Chlamydophila pneumoniae* in blood plasma (conducted according to the package insert for each assay) served as evidence of a qualifying infection

METHODS

Characterization of Isolates

- Clinical study sites were responsible for the identification of pathogens isolated from respiratory and/or blood samples, according to their institution's standard operating procedures
- All pathogens (and plasma samples for serology testing) were required to be shipped to the central laboratory, Eurofins (Lancaster, PA)
  - Isolate identification was confirmed at the central laboratory
  - MIC testing was conducted by broth microdilution according to CLSI M100-S25 and M7-A-10. Custom-made frozen panels from Thermo Fisher Scientific (Cleveland, OH) that contained antimicrobials over a range of doubling dilutions were used
  - Quality control and interpretation of results (susceptible, intermediate, and/or resistant) were performed in accordance with CLSI M100-S25. Quality control results were all within the recommended ranges

RESULTS

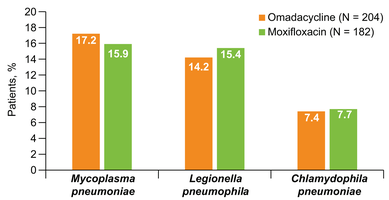
Patient Population

- The microITT population included 204/386 (52.8%) OMC patients and 182/388 (46.9%) MOX patients

Baseline Microbiology

- The most commonly isolated pathogens were *S. pneumoniae* (52/386, 13.5%) and *Haemophilus influenzae* (47/386, 12.2%; **Table 1**)
- Serotype 3 was the most commonly isolated serotype (19% of total *S. pneumoniae*), while less common serotypes varied by region
- The prevalence and resistance profiles of pathogens were similar across treatment groups
  - Macrolide-resistant *S. pneumoniae* occurred in 10/204 (4.9%) OMC patients and in 5/182 (2.7%) MOX patients
  - Multidrug-resistant *S. pneumoniae* occurred in 7/204 (3.4%) OMC patients and in 6/182 (3.3%) MOX patients
  - All but 1 *S. aureus* isolate in the MOX arm were methicillin-sensitive (MSSA)
- Atypical pathogens occurred in 73/204 (35.8%) OMC patients and in 64/182 (35.2%) MOX patients (**Figure 2**)
- Monomicrobial infections were characterized as follows:
  - 37/204 (18.1%) OMC patients and 34/182 (18.7%) MOX patients had monomicrobial Gram-negative infections
  - 30/204 (14.7%) OMC patients and 23/182 (12.6%) MOX patients had monomicrobial Gram-positive infections
- Omadacycline displayed potent activity against Gram-positive aerobes, with an overall MIC_{90} value of 0.12 µg/mL, and the MIC_{90} value against susceptible Gram-negative aerobes ranged from 2 µg/mL for *H. influenzae* to 16 µg/mL for *Klebsiella pneumoniae* (**Table 1**)

Figure 2. Occurrence of atypical pathogens (microITT population).



Note: *M. pneumoniae* and *C. pneumoniae* were identified from serology; *L. pneumophila* was identified from serology or urinary antigen testing.

RESULTS

Table 1. Omadacycline and Moxifloxacin MIC Summary Statistics for Baseline Pathogens From Blood and/or Respiratory Cultures (microITT Population)

	Omadacycline (N = 204)			Moxifloxacin (N = 182)		
Baseline Pathogen	n	Range (µg/mL)	MIC_{50}/ MIC_{90} (µg/mL)	n	Range (µg/mL)	MIC_{50}/ MIC_{90} (µg/mL)
Gram-positive organisms (aerobes)	46	≤0.008 - 0.25	0.06/0.12	45	≤0.03 - 4	0.12/0.25
Streptococcus pneumoniae	28	0.015 - 0.12	0.03/0.06	24	≤0.03 - 0.25	0.12/0.12
MDRSP	7	0.03 - 0.12	—	6	≤0.03 - 0.25	—
PSSP	27	0.015 - 0.12	0.03/0.06	22	0.06 - 0.25	0.12/0.12
Macrolide resistant	10	0.03 - 0.12	0.03/0.06	5	0.06 - 0.25	—
Staphylococcus aureus	11	0.12 - 0.25	0.12/0.25	11	0.03 - 2	0.03/0.06
MSSA	11	0.12 - 0.25	0.12/0.25	10	0.03 - 2	0.03/0.06
Other	11	≤0.008 - 0.12[a]	—	21	0.03 – 4[b]	—
Gram-negative organisms (aerobes)	77	≤0.008 - >16	2/4	65	≤0.004 - >8	0.12/1
Escherichia coli	6	0.5 - 4	—	7	0.03 - >4	—
Haemophilus influenzae	32	0.5 - 4	1/2	15	0.008 - 1	0.03/0.06
Haemophilus parainfluenzae	16	≤0.008 - 4	2/4	16	≤0.004 - >8	0.12/1
Klebsiella pneumoniae	12	1 - 16	2/16	13	0.06 - 0.12	0.12/0.12
Pseudomonas aeruginosa	3	4 - >16	—	5	0.06 - 2	—
Other	17	0.12 - >16[c]	—	19	≤0.03 - >4[d]	—

Abbreviations: MDRSP, multi-drug resistant *S. pneumoniae*; MIC, minimum inhibitory concentration; MRSA, methicillin-resistant *S. aureus*; MSSA, methicillin-susceptible *S. aureus*; N, number of patients in the microITT population; n, number of baseline pathogens with susceptibility data available; PSSP, penicillin-susceptible *S. pneumoniae*.

Note: MRSA and MSSA are considered distinct pathogens. MDRSP, PSSP, and macrolide resistant are considered distinct pathogens. For subjects with the same baseline pathogen in multiple specimens, the pathogen with the highest MIC to the study drug received is used. MIC range is provided for all baseline pathogens. MIC_{50} and MIC_{90} are provided for pathogens isolated at least 10 times in a treatment group.

[a] β-Hemolytic streptococcus (2), *Streptococcus agalactiae* (2), *Streptococcus constellatus* (1), *Streptococcus mitis* (2), *Streptococcus mitis* group (1), *Streptococcus salivarius* (1), *Streptococcus sanguis* II (2).

[b] MRSA (1), β-Hemolytic streptococcus (3), *Streptococcus agalactiae* (3), *Streptococcus anginosus* (1), *Streptococcus constellatus* (1), *Streptococcus gordonii* (1), *Streptococcus mitis* (4), *Streptococcus mitis group* (2), *Streptococcus parasanguinis* (2), *Streptococcus salivarius* (2), *Streptococcus sanguinis* (1).

[c] *Acinetobacter junii* (1), *Acinetobacter lwoffii* (1), *Enterobacter cloacae* (2), *Haemophilus haemolyticus* (1), *Haemophilus parahaemolyticus* (2), *Klebsiella oxytoca* (1), *Moraxella catarrhalis* (4), *Morganella morganii* (1), *Neisseria meningitidis* (1), *Proteus mirabilis* (2), *Serratia marcescens* (1).

[d] *Acinetobacter baumanii* complex (1), *Citrobacter braakii* (1), *Citrobacter freundii* (1), *Enterobacter cloacae* (4), *Haemophilus parahaemolyticus* (2), *Klebsiella oxytoca* (4), *Moraxella catarrhalis* (1), *Neisseria meningitidis* (1), *Proteus mirabilis* (1), *Pseudomonas putida* (1), *Stenotrophomonas maltophilia* (2).

RESULTS

Table 2. Clinical Success at PTE Based on Investigator Assessments by Baseline Pathogen and Study Drug MIC (µg/mL; microITT Population)

	Omadacycline (N = 204)	
Baseline Pathogen	Baseline MIC (µg/mL)	Clinical Success, n/N2 (%)
Gram-positive organisms (aerobes)		
Streptococcus pneumoniae, n/N1		25/28 (89.3)
	0.015	2/2 (100.0)
	0.03	12/14 (85.7)
	0.06	10/10 (100.0)
	0.12	1/2 (50.0)
Staphylococcus aureus, n/N1		8/11 (72.7)
	0.12	6/9 (66.7)
	0.25	2/2 (100.0)
Gram-negative organisms (aerobes)		
Escherichia coli, n/N1		4/6 (66.6)
	0.5	1/1 (100.0)
	1	3/4 (75.0)
	4	0/1 (0.0)
Haemophilus influenzae, n/N1		26/32 (81.3)
	0.5	1/1 (100.0)
	1	16/18 (88.9)
	2	8/12 (66.7)
	4	1/1 (100.0)
Haemophilus parainfluenzae, n/N1		13/16 (81.3)
	≤0.008	1/1 (100.0)
	1	3/4 (75.0)
	2	6/8 (75.0)
	4	3/3 (100.0)
Klebsiella pneumoniae, n/N1		10/12 (83.3)
	1	2/2 (100.0)
	2	5/7 (71.4)
	8	1/1 (100.0)
	16	2/2 (100.0)

Abbreviations: MIC, minimum inhibitory concentration; microITT, microbiologic intent-to-treat; N, number of patients in the microITT population; n, number of patients in the specific category; N1, number of patients in the microITT population with the baseline pathogen; 2, number of patients with the baseline pathogen at the specified MIC.

Percentages are based on the number of patients with the baseline pathogen at the specified MIC.

Patients with the same pathogen identified from blood and/or respiratory cultures are counted only once.

Table contains those pathogens that occurred at least 5 times in one of the treatment groups.

RESULTS

Clinical Outcome

- Clinical success rates were high based on the investigator's assessment at the PTE visit (**Table 2**)
- The MIC of the infecting pathogen at baseline did not influence the clinical outcome, suggesting that target exposure was achieved in the lungs (**Table 2**)
- All 8 patients with tetracycline-resistant *S. pneumoniae* at baseline were treated successfully with OMC

CONCLUSIONS

- In the phase 3 OPTIC study
  - Both the prevalence and resistance profiles of baseline pathogens were similar in the OMC and MOX groups
  - OMC displayed potent *in vitro* activity against the baseline pathogens isolated in this study
  - No correlation was observed between OMC MIC values and clinical outcome, suggesting that target exposure was achieved at the infection site
- Pathogens identified in OPTIC are consistent with those usually seen in patients with CABP[9]
- Overall, in the OPTIC study, monotherapy with IV to once-daily oral OMC was effective in adult CABP patients across the most frequently isolated pathogens, including multi-drug resistant *S. pneumoniae*

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