Susceptibility to Omadacycline in Bone and Joint Infections: Pathogen Susceptibility and Regimen Decisions from an Ongoing Randomized Controlled Trial

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BACKGROUND

- Bone and joint infections (BJI) incidence continues to increase.
- Existing oral BJI antibiotics have limitations
- Omadacycline is a once daily, 3rd generation tetracycline available in oral and IV formulations, approved for use in adults for the treatment of community-acquired pneumonia and skin and soft tissue infections.
- Omadacycline may provide a potential treatment option for BJI due to activity against doxycycline-resistant *S. aureus* and ESBL-producing Enterobacterales for which there are often no viable oral options
- However, characterization of the susceptibility of isolates causing BJI to omadacycline is poorly defined

METHODS

Study Design: Descriptive analysis of isolates from patients enrolled in a multicenter, open-label, non-inferiority randomized controlled trial (ClinicalTrials.gov ID: NCT05753215)

Study Period: May 2022 to April 2025; study ongoing, results reported here represent interim analysis

Study Arms: Standard-of-care (SOC) vs omadacycline-containing regimen

Inclusion Criteria (Abbreviated):

1) Age 18-85
2) BJI or probable BJI caused by or suspected to be caused by organisms that omadacycline is expected to be active against
3) Planned treatment duration of 4-12 weeks in outpatient setting

Exclusion Criteria (Abbreviated):

1) Pregnancy or breastfeeding
2) Hypersensitivity to tetracycline-class antibiotics
3) Prosthetic joint infections that have not undergone both stages of two stages of surgical treatments

Microbiologic methods:

1) Omadacycline susceptibility was assessed on available clinical isolates using MIC Test Strips (Liofilchem®)
2) Susceptibility to omadacycline was interpreted using established FDA breakpoints, although breakpoints for many organisms have not been established

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RESULTS

Table 1. *In-vitro* Susceptibility to Omadacycline of Targeted Isolates of Patients with Bone and Joint Infection

Organism/organism group (no. of isolates)	No. and cumulative % of isolates inhibited at MIC (mg/L) of: 0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	MIC_{50}	MIC_{90}
Gram-positive Organisms												
Streptococcus spp. (40)		3 (8%)	19 (55%)	12 (85%)	6 (100%)						0.25	0.5
Group A *Streptococcus* (1)				1 (100%)							0.25	
Group B *Streptococcus* (28)		2 (7%)	12 (50%)	9 (82%)	5 (100%)						0.12	0.5
Group C *Streptococcus* (4)			2 (50%)	1 (75%)	1 (100%)						0.12	
Group G *Streptococcus* (3)			2 (67%)	1 (100%)							0.12	
Streptococcus anginosus (2)		1 (50%)	1 (100%)								0.06	
Other Viridans group Streptococci (2)			2 (100%)								0.12	
Staphylococcus aureus (36)			2 (6%)	11 (36%)	22 (97%)	1 (100%)					0.5	0.5
MRSA (10)			1 (10%)	5 (60%)	4 (100%)						0.25	0.5
MSSA (26)			1 (4%)	6 (27%)	18 (96%)	1 (100%)					0.5	0.5
Other *Staphylococcus* spp. (2)			1 (50%)	1 (100%)							0.12	
Staphylococcus lugdunensis (1)			1 (100%)								0.12	
Staphylococcus simulans (1)				1 (100%)							0.25	
Corynebacterium striatum (2)				1 (50%)	1 (100%)						0.25	
Cutibacterium acnes (1)		1 (100%)									0.06	
Archaneobacterium spp. (1)			1 (100%)								0.12	
Enterococcus spp. (10)	1 (10%)	1 (20%)	2 (40%)	4 (80%)	1 (90%)		1 (100%)				0.25	0.5
Enterococcus avium (1)		1 (100%)									0.06	
Enterococcus faecalis (9)	1 (11%)		2 (33%)	4 (78%)	1 (89%)		1 (100%)				0.25	
Gram-negative Organisms												
E. coli. (14)					2 (14%)	6 (57%)	2 (71%)	1 (79%)		3 (100%)	1	16
E. coli, ESBL (5)						1 (20%)	1 (40%)	1 (60%)		2 (100%)	4	
E. coli, non-ESBL (9)					2 (22%)	5 (78%)	1 (89%)			1 (100%)	1	
Klebsiella spp. (9)					1 (11%)	1 (22%)	5 (78%)	1 (89%)	1 (100%)		2	
Klebsiella aerogenes (1)							1 (100%)				1	
Klebsiella oxytoca (3)						1 (33%)	2 (100%)				2	
Klebsiella pneumoniae, ESBL (2)							1 (50%)		1 (100%)		2	
Klebsiella pneumoniae, non-ESBL (3)					1 (33%)		1 (67%)	1 (100%)			2	
Citrobacter spp. (4)[a]					1 (25%)	3 (100%)					1	
Stenotrophomonas maltophilia (3)						2 (67%)	1 (100%)				1	
Enterobacter cloacae (3)			1 (33%)				1 (67%)	1 (100%)			2	
Achromobacter spp. (2)									1 (50%)	1 (100%)	8	
Alcaligenes faecalis (1)									1 (100%)		8	
Acinetobacter baumannii complex (1)					1 (100%)						0.5	
Aeromonas spp. (1)						1 (100%)					1	
Raoutella spp. (1)								1 (100%)			4	

Color coding represents susceptible, intermediate, and resistant breakpoints according to FDA approved breakpoints for the acute bacterial skin and skin structure infection indication. No color coding indicates that FDA breakpoints are not established for these organisms.
[a]Organisms include: *Citrobacter koseri, Citrobacter freundii* complex, and *Citrobacter koseri*
MRSA*:* methicillin-resistant *Staphylococcus aureus;* MSSA*:* methicillin-susceptible *Staphylococcus aureus;* ESBL: extended-spectrum beta-lactamases

Table 2. Demographics and Bone and Joint Infection Types

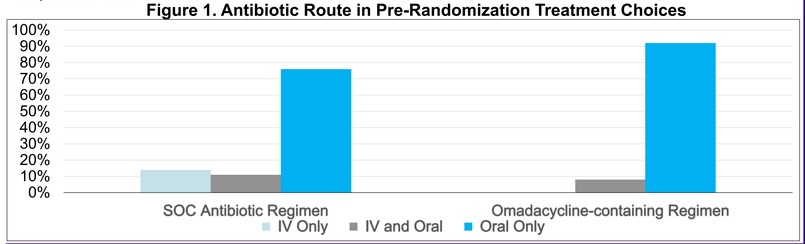
	Enrolled Patients (n=132)
Age (median, IQR)	(56, 48-61)
Gender (n, %)	
Male	117 (89%)
Female	15 (11%)
BJI Types (n, %)	
Diabetic foot infection with osteomyelitis	112 (85%)
Orthopedic hardware infection	8 (6%)
Prosthetic joint infection	7 (5%)
Osteomyelitis, non-prosthetic, non-diabetic foot	5 (4%)

Table 3. Pre-Randomization Treatment Choices

Pre-Randomization Treatment	If Patient to be Randomized SOC Antibiotic Regimen (n=132)	If Patient to be Randomized Omadacycline-containing Regimen (n=132)
Antibiotics* (n, %)		
Omadacycline	0 (0%)	132 (100%)
Amoxicillin-clavulanic acid	47 (36%)	15 (11%)
Doxycycline	49 (37%)	0 (0%)
Ciprofloxacin	26 (20%)	20 (15%)
Levofloxacin	12 (9%)	19 (14%)
Metronidazole	13 (10%)	10 (8%)
Ceftriaxone	13 (10%)	7 (5%)
Trimethoprim-sulfamethoxazole	13 (10%)	1 (1%)
Ertapenem	8 (6%)	2 (2%)
Cefepime	4 (3%)	3 (2%)
Amoxicillin	1 (1%)	5 (4%)
Daptomycin	5 (4%)	1 (1%)
Clindamycin	4 (3%)	0 (0%)
Cefdinir	2 (2%)	1 (1%)
Linezolid	2 (2%)	1 (1%)
Vancomycin	3 (2%)	0 (0%)
Rifampin	1 (1%)	1 (1%)
Cefazolin	2 (2%)	0 (0%)
Oxacillin	1 (1%)	0 (0%)

*Participants could receive more than one antibiotic. SOC: Standard-of-care

Figure 1. Antibiotic Route in Pre-Randomization Treatment Choices



CONCLUSION

- In our randomized trial of BJI treatment, omadacycline demonstrated in vitro activity against most BJI pathogens, including *Streptococcus*, MRSA, and Enterobacterales
- Majority of patients were male, and most common type of bone and joint infections were diabetic foot infections. A higher proportion of omadacycline-containing regimens were eligible for oral-only therapy compared to standard-of-care
- Continued investigation is warranted for consideration of omadacycline as a potential oral option in BJI