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Efficacy of Omadacycline against Molecularly Characterized Gram-Positive and Gram-Negative Pathogens Causing Infections in the Phase 3 CABP and ABSSI Clinical Trials

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Introduction

- Omadacycline represents a new class of tetracycline-related compounds, the aminomethylcyclines, that possesses antibacterial activity from its ability to bind to the 30S subunit of the bacterial ribosome and inhibit bacterial protein synthesis
- Structural modifications at the C-7 and C-9 positions allow omadacycline to overcome the 2 main mechanisms of resistance to tetracyclines: efflux pumps and ribosomal protection (see poster #1377)
- One phase 3 trial for community-acquired bacterial pneumonia (CABP; OPTIC) and 2 phase 3 trials for acute bacterial skin and skin structure infections (ABSSSIs; OASIS-1 and OASIS-2) were completed
- This study provided the molecular characterization of clinical trial isolates and evaluated the efficacy results of omadacycline against subsets of macrolide or doxycyclinenonsusceptible isolates

Materials and Methods

Bacterial organisms

- Gram-positive (n=24) and -negative (n=17) clinical isolates recovered from subjects enrolled in the OPTIC (n=26), OASIS-1 (n=10), or OASIS-2 (n=5) trials were selected for molecular characterization and included in this investigation
- Gram-positive isolates were selected based on the presence of tetracycline and/or macrolide resistance phenotypes; Gram-negative isolates were selected based on nonsusceptibility to tetracycline

Antimicrobial susceptibility testing

'Adapted from http://faculty.washington.edu/marilynr/ermwebA.pdf.

 Selected isolates were tested for antimicrobial susceptibility using 96-well frozenform broth microdilution panels containing cation-adjusted Mueller-Hinton broth and panels were manufactured per the Clinical and Laboratory Standards Institute (CLSI) specifications described in the M07-A10 (2015) document

- MIC values were validated by concurrently testing the appropriate gram-positive and -negative strains recommended by the CLSI M100 documents
- MIC results obtained against ATCC quality-control strains were interpreted according to published criteria per CLSI M100 guidelines
- MIC values obtained against clinical isolates were interpreted using published CLSI (M100, 2017) breakpoints, when available

Characterizing tetracycline resistance mechanisms

- Whole genome extraction and sequencing
- Selected isolates had total genomic DNA extracted by the fully automated Thermo Scientific™ KingFisher™ Flex Magnetic Particle Processor (Cleveland, Ohio, USA), which was used as input material for library construction
- DNA libraries were prepared using the Nextera™ library construction protocol (Illumina, San Diego, CA, USA) following the manufacturer's instructions and were sequenced on a MiSeq Sequencer (JMI Laboratories, North Liberty, Iowa, USA)
- Sequence analysis
- FASTQ format sequencing files for each sample set were assembled independently using de novo assembler SPAdes 3.9.0, and an in-house designed software pipeline was applied to align the assembled sequences against numerous determinants associated with MLS_R phenotype (including rRNA methylases, efflux pumps, and inactivating enzymes) and tetracycline resistance (such as ribosomal protection, enzymatic, and efflux pumps) (Table 1)
- Multilocus sequence typing (MLST) was performed by extracting previously defined sets of 7 housekeeping gene fragments (~500 bp) for each species included in the study and each fragment was compared to known allele variants for each locus (housekeeping gene) on the MLST website (http://www.mlst.net)

Efficacy analysis

 The efficacy endpoint was investigator's assessment of clinical response at post therapy evaluation (PTE)

Table 2 Summary of results obtained from S. pneumoniae clinical trial isolates

laalata	C4dv.	Source isolate	Macrolide resistance		MLST			MIC (µ	Treatment	Clinical			
Isolate	Study	no.	determinant(s) ^a	ST	Profile	OMC	AZI	ERY	CLI	DOX	TET	arm	outcome ^b
6	CABP	D604669	erm(B), tet(M)	ST62	2-5-29-12-16-3-14	0.06	>1	>0.5	>0.5	>8	>4	OMC	Success
7	CABP	E101733	erm(B), tet(M)	ST62	2-5-29-12-16-3-14	0.03	>1	>0.5	>0.5	8	>4	MXF	Success
8	CABP	E101737	erm(B), tet(M)	ST179	7-14-40-12-1-1-14	0.03	>1	>0.5	>0.5	8	>4	OMC	Success
9	CABP	D604807	mef(A), msr(D)	ST13568	1-5-4-5-587-1-8	0.03	>1	>0.5	0.06	0.12	0.25	OMC	Success
10	CABP	D606264	mef(A), msr(D)	ST9	1-5-4-5-5-1-8	0.03	>1	>0.5	0.12	0.12	0.25	OMC	Success
11	CABP	D759414	erm(B), tet(M)	ST180	7-15-2-10-6-1-22	0.06	>1	>0.5	0.12	8	>4	MXF	Success
13	CABP	E052867	erm(B), mef(A), msr(D), tet(M)	ST320	4-16-19-15-6-20-1	0.03	>1	>0.5	>0.5	2	>4	MXF	Success
14	CABP	D780411	mef(A), msr(D)	ST100	5-12-29-12-9-39-18	0.03	>1	>0.5	0.06	0.06	0.12	OMC	Success
15	CABP	D791162	erm(B), tet(M)	ST2467	7-25-4-1-15-20-28	0.03	>1	>0.5	>0.5	2	>4	OMC	Success
16	CABP	D826829	erm(B), tet(M)	ST2744	7-6-9-2-6-1-68	0.06	>1	>0.5	>0.5	8	>4	OMC	Success
17	CABP	E216193	erm(B), tet(M)	ST13570	1-597-1-8-11-5-11	0.06	>1	>0.5	>0.5	>8	>4	OMC	Success
18	CABP	D818811	erm(B), tet(M)	ST4310	32-28-1-1-15-1-14	0.03	>1	>0.5	>0.5	8	>4	OMC	Success
19	CABP	D735404	tet(M)	ST2031	7-8-53-6-10-6-14	0.06	0.5	0.06	0.12	4	>4	OMC	Success
20	CABP	E141031	mef(A), msr(D), tet(M)	ST719	15-29-2-21-30-1-14	0.03	>1	>0.5	0.06	8	>4	MXF	Success
21	CABP	E140987	mef(A), msr(D), tet(M)	ST1611	2-19-2-17-15-22-14	0.03	>1	>0.5	0.12	4	>4	MXF	Success
27	ABSSSI	TR2011200870	erm(B), tet(M)	ST180	7-15-2-10-6-1-22	0.03	>1	>0.5	>0.5	0.06	0.12	OMC	Success

CABP, community-acquired bacterial pneumonia; MLST, multilocus sequence typing; OMC, omadacycline; AZI, azithromycin; ERY, erythromycin; DOX, doxycycline; TET, tetracycline; MXF, moxifloxacin; ABSSSI, acute bacterial skin and skin structure infection.

^a Listed gene or a variant with >99% identity detected in each case. *tet*(M) detected in isolate TR2011200870 had a premature stop codon.

^b The efficacy endpoint was investigator's assessment of clinical response at post therapy evaluation.

Table 3 Summary of results obtained from *S. aureus* clinical trial isolates

looloto	Ctudy	Source isolate	Magralida registares determinant/o\a		MLST			Treetment eve	Clinical			
Isolate	Study	no.	Macrolide resistance determinant(s) ^a	ST	Profile	OMC	AZI	ERY	CLI	DOX	Treatment arm	outcomeb
1	ABSSSI	R4091141	tet(38), tet(K)	ST8	3-3-1-1-4-4-3	0.25	2	0.5	0.12	8	OMC	Success
2	ABSSSI	R6041266	tet(38), tet(M), erm(C)	ST8	3-3-1-1-4-4-3	0.5	>4	>4	>4	8	LZD	Success
4	ABSSSI	R7212058	tet(38), tet(M), mph(C), msr(A)	ST8	3-3-1-1-4-4-3	0.25	8	>4	0.12	8	LZD	Success
5	CABP	D665005	tet(38), tet(M), tet(L)	ST8	3-3-1-1-4-4-3	0.25	1	0.25	0.12	16	MXF	Success
22	ABSSSI	D661166	tet(38), tet(M)	ST3081°	3-4-1-4-12-1-10	0.25	2	0.5	0.12	8	LZD	Success
24	ABSSSI	EJ14045	tet(38), tet(M), erm(C), mph(C), msr(A)	ST8	3-3-1-1-4-4-3	0.25	>4	>4	>4	8	LZD	Success
25	ABSSSI	EJ29451	tet(38), tet(M)	ST4302	1-648-1-8-11-5-11	0.25	2	0.5	0.12	8	LZD	Indeterminate
26	ABSSSI	EJ03946	tet(38), tet(M)	ST4302	1-648-1-8-11-5-11	0.25	2	0.5	0.12	8	LZD	Indeterminate

ABSSSI, acute bacterial skin and skin structure infection; MLST, multilocus sequence typing; OMC, omadacycline; AZI, azithromycin; CLI, clindamycin; DOX, doxycycline; MXF, moxifloxacin; LZD, linezolid; CABP, community-acquired bacterial pneumonia. ^a Listed gene or a variant with >99% identity was detected in each case; *tet*(38) is intrinsic in *S. aureus*.

^b The efficacy endpoint was investigator's assessment of clinical response at post therapy evaluation.

^c ST3081 is single locus variant (SLV) of ST5, while ST37 is a SLV of ST36.

Table 1 Genes associated with the MLS_R and tetracycline resistance phenotype investigated

		Resistance genes encod	ling fora:		
MLS _B			Inactivati	ing enzymes	
rRNA methylase	Efflux	Esterase	Lyases	Transferases	Phosphorylases
erm(A), (B), (C), (D), (E), (F), (G), (H), (I), (N), (O), (Q), (R), (S), (T), (U), (V), (W), (X), (Y), (Z), (30), (31), (33), (32), (33), (34), (35), (36), (37), (38), (39), (40), (41), (42), (43), (44), (45), (46)	tlr(C) lsa(A), (B), (C), (E) vga(A), (B), (C), (D), (E) vgb, vgb(A), (B) eat(A) sal(A) mac(A), (B) mre(A)	ere(A), (A2), (B), (D)	vgb(A), (A)LC, (B)	Inu(A), (A'), (AN2), (B), (C), (D), (E (F), (P) vat(A), (B), (C) vat(D), (E), (F), (H) mgt ole(B), (C), (D), (I) lin	mph(A), (B), (C), (D), (E), (F), (G)
cfr, cfr(B), cfr(C), myr(A), tsn(R),					
Tetracycline	Efflux	Ribosomal protection	Enzymatic	Unknown	
	tet(A), tet(B), tet(C), tet(D), tet(E), tet(59), tet(G), tet(H), tet(J), tet(V), tet(Y), tet(Z), tet(30), tet(31), tet(33), tet(57), tet(35), tet(39), tet(41), tet(K), tet(L), tet(38), tet(45), tet(58), tetA(P), tet(40), otr(B), otr(C), ter, tet(42), tet(43), tetAB(46), tetAB(60)	tet(Q), tet(T), tet(36), otr(A),	tet(X), tet(37), tet(34), tet(47), tet(48), tet(49), tet(50), tet(51), tet(52), tet(53), tet(54), tet(55), tet(56)	tet(U)	

Table 4 Summary of results obtained from gram-negative clinical trial isolates

Isolate	Study	Source isolate no.	Organism	404 00000	MLST				Two of two or of the two	Clinical			
				tet gene ^a	ST	Profile	OMC	TIG	DOX	MIN	TET	Treatment arm	outcomec
2	ABSSSI	D661170	E. coli	tet(A)	372	17-88-103-19-36-23-44-26	2	0.25	8	1	>16	LZD	Success
10	ABSSSI	EJ03755	E. coli	tet(A)	131	53-40-47-13-36-28-29	1	0.25	8	2	>16	OMC	Success
16	CABP	D670591	E. coli	tet(A)	131	53-40-47-13-36-28-29	2	0.25	8	2	>16	OMC	Indeterminate
17	CABP	D826823	E. coli	tet(A)	131	53-40-47-13-36-28-29	1	0.25	8	2	>16	MXF	Success
22	CABP	D604732	E. coli	tet(B)	73	36-24-9-13-17-11-25	1	0.25	>8	32	>16	OMC	Success
30	ABSSSI	D873248	E. coli	tet(B)	744	10-11-135-8-8-2	0.5	0.12	>8	8	>16	LZD	Success
31	CABP	EK21636	E. coli	tet(A), tet(B)	744	10-11-135-8-8-2	2	0.25	>8	8	>16	MXF	Success
32	CABP	D658102	E. coli	tet(A)	NA^b	6-4-12-1-20-18-7	2	0.25	>8	2	>16	MXF	Success
4	ABSSSI	D648088	E. cloacae	tet(D)	NA	59-40-6-9-62-6-6	2	0.5	>8	32	>16	OMC	Success
6	ABSSSI	D687070	E. cloacae	tet(D)	419	59-9-86-9-67-37-6	2	0.5	>8	32	>16	OMC	Success
8	ABSSSI	D873239	K. pneumoniae	tet(A)	17	2-1-1-4-4-4	2	0.5	>8	4	>16	LZD	Success
13	CABP	D665009	K. pneumoniae	tet(A)	307	4-1-2-52-1-1-7	8	1	>8	8	>16	OMC	Failure
19	CABP	D944286	K. pneumoniae	tet(A)	23	2-1-1-1-9-4-12	16	2	>8	>32	>16	OMC	Success
20	CABP	D736002	K. pneumoniae	tet(A)	NA	2-3-2-1-10-1-43	4	1	>8	8	>16	OMC	Success
21	CABP	D736023	K. pneumoniae	tet(A)	NA	2-3-2-1-10-1-43	8	1	>8	4	>16	MXF	Success
25	CABP	D969351	K. pneumoniae	tet(A)	1	4-4-1-1-7-4-10	16	2	>8	32	>16	OMC	Success
28	ABSSSI	R7081262	K. pneumoniae	ND	14	1-6-1-1-1	8	4	>8	16	>16	LZD	Success

ABSSSI, acute bacterial skin and skin structure infection; MLST, multilocus sequence typing; OMC, omadacycline; TIG, tigecycline; MIN, minocycline; TET, tetracycline; MXF, moxifloxacin; LZD, linezolid; CABP, community-acquired bacterial pneumonia. ^a ND, *tet* genes investigated were not detected. Wild-type *rpsJ* (S10 rRNA) sequences were observed in all isolates.

b NA, ST not assigned vet for this profile. The efficacy endpoint was investigator's assessment of clinical response at post therapy evaluation.

Results

- All but 1 S. pneumoniae carried MLS_B-associated genes, while tetracycline- and doxycycline-nonsusceptible isolates (n=12) had *tet*(M) (Table 2)
- S. aureus (8 isolates) exhibited a doxycycline-nonsusceptible phenotype (MIC,
- 8-16 µg/mL) and omadacycline MIC values of 0.25-0.5 µg/mL (Table 3)
- All S. aureus carried tet(M), except for 1 isolate with a tet(K) gene and 1 isolate with tet(M) and tet(L) genes (Table 3)
- All Escherichia coli (8 isolates; omadacycline MIC, 0.5–2 μg/mL), Enterobacter cloacae (2 isolates; omadacycline MIC, 2 μg/mL), and Klebsiella pneumoniae (6 isolates; omadacycline MIC, 2–16 µg/mL) carried tetracycline efflux-pump genes, tet(A) and/or tet(B), tet(D), and tet(A) (omadacycline MIC, 0.03–0.06 μg/mL), respectively (Table 4)
- tet genes were not detected in 1 K. pneumoniae (omadacycline MIC, 8 μg/mL) isolate
- A total of 3 E. coli isolates belonged to the epidemic ST131 lineage (Table 4)
- Clinical success was noted in 14/16 (87.5%) omadacycline-treated subjects in OPTIC, and 5/5 (100%) omadacycline-treated subjects in the combined OASIS studies
- All omadacycline-treated subjects with S. pneumoniae at baseline had outcomes of clinical success at PTE
- Two linezolid-treated subjects with Staphylococcus aureus (omadacycline MIC, 0.25 µg/mL) from OASIS-1 and 1 omadacycline-treated subject from OPTIC with E. coli (omadacycline MIC, 2 μg/mL) had indeterminate clinical responses at PTE
- One omadacycline-treated subject from OPTIC with K. pneumoniae (omadacycline MIC, 8 μg/mL) was a clinical failure at PTE

- Omadacycline demonstrated clinical success regardless of MIC result or presence of tetracycline and/or MLS_R resistance mechanisms
- This study expands on the analysis of omadacycline efficacy data among subjects infected with nonsusceptible pathogens

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