

Abstract

Background: Omadacycline (OMC) is the first aminomethylcycline in late stage clinical development for CABP and ABSSI as oral and IV, once-daily formulations. The *in vitro* activity against a variety of *L. pneumophila* isolated from 1995 to 2005 and from 2006 to 2014 was investigated to determine whether any change in susceptibility has occurred.

Methods: The *in vitro* activity of OMC was compared with that of doxycycline (DO), telithromycin (TE), azithromycin (AZ), erythromycin (ER), levofloxacin (LE) and moxifloxacin (MO) against a total of 50 *L. pneumophila* isolates from 1995 to 2005 (serogroup 1 (n=45) and serogroup 2, 3, 4, 5 and 6 (n=1 for each serogroup)) and against a total of 50 *L. pneumophila* isolates from 2006 to 2014 by microdilution procedure using buffered yeast extract broth containing *Legionella* growth supplement (BYE). A pre-test to determine if antibiotic activity was impacted artificially by *Legionella* supplement or iron was done by testing three ATCC quality control isolates on BYE, BYE without iron and cation-adjusted Mueller-Hinton Broth (MH).

Results: The MIC_{50/90} values of OMC (0.25/0.25) compared to MO (0.008/0.016), LE (0.016/0.016), TE (0.03/0.06), AZ (0.12/0.5), ER (0.12/1) and DO (1/1 mg/L) against tested *L. pneumophila* serogroup 1 isolates from 1995 to 2005 were comparable to the MIC_{50/90} values obtained by *L. pneumophila* serogroup 1 from 2006 to 2014 (OMC (0.25/0.25), MO (0.008/0.016), LE (0.016/0.016), TE (0.03/0.06), AZ (0.12/ 0.5), ER (0.25/1) and DO (1/1 mg/L)). Against all tested *L. pneumophila* isolates from 1995 to 2014, the MIC_{50/90} of MO, LE, TE, OMC, AZ, ER and DO was 0.008/0.016, 0.016/0.016, 0.03/0.06, 0.25/0.25, 0.06/0.5, 0.25/1 and 1/1 mg/L respectively.

Pilot tests indicated that BYE resulted in a 5- to 7-fold increase in MICs for OMC and DO relative to MH for *S. aureus* ATCC29213 and *E. coli* ATCC25922. This suggests that the MIC values of OMC and DO obtained in BYE for *L. pneumophila* may be artificially elevated due to the media effects.

Conclusions: The activity of OMC has not changed between the 1995-2005 isolates and the 2006-2014 isolates. This data suggest that OMC may have use in infections caused by *L. pneumophila* and highlights the potential utility of this oral and IV agent for the treatment of CABP.

Introduction

Omadacycline is the first aminomethylcycline to be developed as a once daily, oral and IV treatment of Acute Bacterial Skin and Skin Structure Infection (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP). The Phase 3 development program has now been initiated. **Omadacycline** has excellent activity against the primary pathogens associated with ABSSSI and CABP, including antibiotic resistant organisms, including *S. aureus*, β -hemolytic *streptococci*, *S. pneumoniae*, *H. influenzae*, *Legionella* and *C. pneumoniae*.

Objective

The goal of this study was to investigate the activity of **omadacycline** against a variety of *Legionella pneumophila* isolated from 1995 to 2005 and from 2006 to 2014. We determined the minimum inhibitory concentration (MIC) of **omadacycline**, doxycycline, telithromycin, azithromycin, erythromycin, levofloxacin and moxifloxacin to evaluate whether any change in susceptibility has occurred between the two *L. pneumophila* group.

Materials and Methods

Strains

A total of 50 strains of *L. pneumophila* isolated from 1995 to 2005 (serogroup 1 (n=45) and serogroup 2, 3, 4, 5 and 6 (n=1 each serogroup)) and a total of 50 *L. pneumophila* isolates from 2006 to 2014 were collected from mostly nosocomial or acquired respiratory tract sources and were identified by standard methods such as described by Versalovic et al. (1).

Determination of MICs

MICs were determined using the CLSI broth medium microdilution method using microdilution plating of the organisms onto a series of broth medium microplates of increasing concentrations from 0.004 mg/L to 128 mg/L (2, 3). Buffered Yeast extract (BYE) was used as the medium against *Legionella* strains. *Staphylococcus aureus* ATCC29213, *Pseudomonas aeruginosa* ATCC27853 and *L. pneumophila* ATCC33152 were included as controls.

Growth conditions

S. aureus ATCC29213, *E. coli* ATCC25922, *P. aeruginosa* ATCC27853 and *L. pneumophila* ATCC33152 were tested in a media testing study comparing the activities of antibiotics in cation adjusted Mueller Hinton Broth (MH), standard BYE, and modified BYE ("Mod BYE"; lacking ferric pyrophosphate). Only data for *E. coli* and *L. pneumophila* is shown in Table 1.

Results

Table 1. Media Study: Susceptibility of QC strain: *Escherichia coli* ATCC25922 & *Legionella pneumophila* ATCC33152

QC Strain & Incubation time	Media tested	Antibiotic MIC (mg/L)				
		Omadacycline	Doxycycline	Telithromycin	Azithromycin	Erythromycin
<i>E. coli</i> ATCC25922 24 hours	Cation adjusted M-H	1	2	32	>128	>128
	Modified BYE	16	0.5	>128	>128	>128
	BYE	32	64	32	>128	>128
48 hours	Cation adjusted M-H	Not Done	Not Done	Not Done	Not Done	Not Done
	Modified BYE	16	1	>128	>128	>128
	BYE	128	>128	128	>128	>128
Expected MIC range	Cation adjusted M-H	0.25-2*	0.5-2*	Unknown	Unknown	Unknown
<i>L. pneumophila</i> ATCC33152 24 hours	Cation adjusted M-H	No Growth	No Growth	No Growth	No Growth	No Growth
	Modified BYE	No Growth	No Growth	No Growth	No Growth	No Growth
	BYE	No Growth	No Growth	No Growth	No Growth	No Growth
48 hours	Cation adjusted M-H	No Growth	No Growth	No Growth	No Growth	No Growth
	Modified BYE	No Growth	No Growth	No Growth	No Growth	No Growth
	BYE	0.25	1	0.03	0.06	0.25

* Expected MIC Range with Cation adjusted Mueller-Hinton, data obtained from CLSI

Results continued

Table 2. Susceptibility of *Legionella pneumophila* all tested serogroup and *L. pneumophila* serogroup 1 (from 1995 to 2014; from 1995 to 2005 and from 2006 to 2014)

Organism (no. tested)	Collection Date	Antibiotic	MIC (mg/L)		
			Range	50%	90%
<i>Legionella pneumophila</i> all serogroup (100 strains)	From 1995-2014	Omadacycline	0.06-1	0.25	0.25
		Doxycycline	0.5-1	1	1
		Telithromycin	0.016-0.12	0.03	0.06
		Azithromycin	0.008-0.5	0.12	0.5
		Erythromycin	0.06-2	0.25	1
		Levofloxacin	≤0.004-0.03	0.016	0.016
<i>Legionella pneumophila</i> serogroup 1 (90 strains)	From 1995-2014	Omadacycline	0.06-0.5	0.25	0.25
		Doxycycline	0.5-1	1	1
		Telithromycin	0.016-0.12	0.03	0.06
		Azithromycin	0.016-0.5	0.12	0.5
		Erythromycin	0.06-2	0.25	1
		Levofloxacin	≤0.004-0.03	0.016	0.016
<i>Legionella pneumophila</i> serogroup 1 (45 strains)	From 1995-2005	Omadacycline	0.06-0.5	0.25	0.25
		Doxycycline	0.5-1	1	1
		Telithromycin	0.016-0.12	0.03	0.06
		Azithromycin	0.016-0.5	0.12	0.5
		Erythromycin	0.06-2	0.12	1
		Levofloxacin	0.008-0.03	0.016	0.016
<i>Legionella pneumophila</i> serogroup 1 (45 strains)	From 2006-2014	Omadacycline	0.06-0.5	0.25	0.25
		Doxycycline	0.5-1	1	1
		Telithromycin	0.016-0.06	0.03	0.06
		Azithromycin	0.016-0.5	0.12	0.5
		Erythromycin	0.06-2	0.25	1
		Levofloxacin	≤0.004-0.06	0.016	0.016
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		Azithromycin	0.016-0.5	0.12	0.5
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