

In Vitro Antimicrobial Activity of Omadacycline, a New Aminomethylcycline, Against Gram-Positive and Gram-Negative Bacterial Pathogens Isolated from Patients Attending Canadian Hospitals in 2015; the CANWARD Study

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ABSTRACT

Background: Omadacycline (OMC) has the potential to be the first agent in a new antibacterial class, the aminomethylcyclines. OMC is a semisynthetic derivative of minocycline and is being developed in both intravenous and oral formulations. Based on its microbiological and pharmacological profiles, OMC is being developed as a broad-spectrum agent for the once daily treatment of patients with acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, and other types of community-acquired bacterial infections.

Methods: CANWARD was initiated in 2007 and is a national, annual, surveillance study assessing bacterial pathogens causing infection in patients attending tertiary-care Canadian hospital clinics (HCs), emergency rooms (ERs), medical and surgical wards (MSWs), and intensive care units (ICUs) and their antimicrobial resistance phenotypes. Isolates included in the current study were from CANWARD 2015; their specimen source composition was respiratory (40.2%), blood (39.6%), urine (10.1%), and wound (10.1%). Isolate associated demographic characteristics were: patient gender (male/female [53.9/46.1%]), patient age (\leq 17/18-64/ \geq 65 years [14.0/42.3/43.7%]), and patient location (MSWs/ERs/HCs/ICUs [41.1/22.0/19.2/17.6%]). The most common pathogens identified were: *E. coli* (EC), methicillin-susceptible *S. aureus* (MSSA), *P. aeruginosa* (PA), *S. pneumoniae* (SPN), *K. pneumoniae* (KP), *E. faecalis* (EF), methicillin-resistant *S. aureus* (MRSA), and *H. influenzae* (HI). Antimicrobial susceptibility testing of OMC and marketed comparators was performed using the standard CLSI broth microdilution method (M07-A10, 2015).

Results: MIC_{50/90} (µg/ml) values for OMC and tigecycline were: 0.5/2 versus 0.25/0.5, respectively, for EC; 0.25/0.5 versus 0.12/0.25 for MSSA; >16/>16 versus >16/>16 for PA; 0.06/0.06 versus 0.03/0.03 for SPN with similar activity versus penicillin-resistant isolates; 2/8 versus 1/2 for KP; 0.12/0.12 versus 0.12/0.12 for EF and *E. faecium* including VRE; 0.25/0.5 versus 0.12/0.25 for MRSA with similar activity against community-associated (CA) and healthcare-associated (HA) genotypes, and 0.5/1 versus 0.5/1 for HI.

Conclusions: OMC was a broad-spectrum agent with potent activity against both Gram-positive and Gram-negative pathogens. OMC was active against tetracycline-resistant and MDR Gram-positive organisms including MRSA (CA and HA genotypes), penicillin-resistant and MDR SPN, and VRE as well as frequent Gram-negative pathogens (EC, KP, HI).

INTRODUCTION

Omadacycline (OMC) is the first agent in a new antibacterial class, the aminomethylcyclines (1-5). OMC is a semisynthetic derivative of minocycline and is available in both intravenous and oral formulations. Based on its microbiological and pharmacological profiles, OMC is being developed as a broad-spectrum agent for the once daily treatment of patients with acute bacterial skin and skin structure infections, community-acquired bacterial pneumonia, and other types of community-acquired bacterial infections.

The purpose of this study was to assess the activity of omadacycline and comparators against isolates obtained from patients in Canadian hospitals as part of the CANWARD 2015 study.

METHODS

Study Background - CANWARD

The isolates tested in this study were obtained from January 2015 to October 2015, inclusive, from an ongoing cross-Canada surveillance study (CANWARD study; <u>www.can-r.ca</u>) (6). The goal of the CANWARD 2015 study was to assess pathogens and antimicrobial resistance patterns associated with lower respiratory tract, skin/skin structure, urinary, and bacteremic infections in Canadian patients on medical wards, surgical wards, intensive care units, and presenting to emergency rooms and hospital clinics (6).

Bacterial Isolates

From January 2015 through October 2015, inclusive, each of 13 study sites was asked to submit clinical isolates (consecutive, one per patient) from inpatients and outpatients with respiratory, urine, wound, and bloodstream infections. The medical centres submitted "clinically significant" isolates from patients with a presumed infectious disease. Surveillance swabs, eye, ear, nose and throat swabs were excluded. We also excluded anaerobic organisms. Isolate identification was performed by the submitting site and confirmed at the reference site as required, based on morphological characteristics and antimicrobial susceptibility patterns. Isolates were shipped on Amies semi-solid transport media to the coordinating laboratory (Health Sciences Centre, Winnipeg, Canada), subcultured onto appropriate media, and stocked in skim milk at -80°C until minimum inhibitory concentration (MIC) testing was carried out.

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METHODS (CONT.)

Antimicrobial Susceptibilities

Following 2 subcultures from frozen stock, the *in vitro* activity of selected antimicrobials was determined by broth microdilution in accordance with the Clinical and Laboratory Standards Institute (CLSI) guidelines (CLSI, 2015 M7-A10). Antimicrobial minimum inhibitory concentration (MIC) interpretive standards were defined according to CLSI breakpoints (M100S, 2015). Antimicrobial agents were obtained as laboratory grade powders from their respective manufacturers. Stock solutions were prepared and dilutions made as described by CLSI (M7-A10, 2015). The MICs of the antimicrobial agents for the isolates were determined using 96-well custom designed microtitre plates. These plates contained doubling antimicrobial dilutions in 100µl/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10⁵ CFU/mI then incubated in ambient air for 24 hours prior to reading. Colony counts were performed periodically to confirm inocula. Quality control was performed using ATCC QC organisms including: *S. pneumoniae* 49619, *S. aureus* 29213, *E. faecalis* 29212, *E. coli* 25922, and *P. aeruginosa* 27853.

Participating Centres and Site Investigators

Vancouver Hospital, Vancouver, BC – Dr. D. Roscoe; University of Alberta Hospitals, Edmonton, AB – Dr. R. Rennie; Royal University Hospital, Saskatoon, SK – Dr. J. Blondeau; Health Sciences Centre, Winnipeg, MB – Drs. D. Hoban/G. Zhanel; Mount Sinai Hospital, Toronto, ON – Dr. S. Poutanen; Children's Hospital of Eastern Ontario, Ottawa, ON – Dr. F. Chan; London Health Sciences Centre, London, ON – Dr. M.John; Centre Hospitalier Universitaire Sherbrooke, Sherbrooke, QC – Dr. A. Carignan; CHRTR Pavillon Ste. Marie, Trois-Rivières, QC – Dr. M. Goyette; Hôpital Cite-de-la-Santé, Laval, QC – Dr. M. Bergevin; L'Hôtel-Dieu de Québec, Québec City, QC – Dr. R. Pelletier; South East Regional Health Authority – Moncton, NB – Dr. M. Kuhn; QEII Health Sciences Centre, Halifax, NS – Dr. R. Davidson

CONCLUSIONS

- Omadacycline is active versus Gram-positive cocci including methicillin-susceptible, methicillinresistant *S. aureus* (MRSA, including both community-acquired and healthcare-acquired), *Streptococcus pneumoniae* including penicillin-resistant strains and *Enterococcus* spp., including vancomycin-resistant Enterococci (VRE).
- Omadacycline is active versus *Enterobacteriaceae* such as *E. coli* (including ESBL-producing strains), *Klebsiella* spp. (including ESBL-producing strains) as well as *Haemophilus influenzae*.
- Omadacycline demonstrates limited/poor activity versus P. aeruginosa.
- OMC was a broad-spectrum agent with potent activity against both Gram-positive and Gramnegative pathogens.

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TABLE 1. Omadacycline <i>in vitro</i>		99 aerobic	Gram-pos	sitive bac	cteria isola
from patients in Canadian hospi	tals in 2015				
Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC Range	µg/ml MIC₅₀	MIC ₉₀	— % Susceptik
Methicillin-susceptible <i>S. aureus</i> (604)		0.06-2	0.25	0.5	NB
	Omadacycline Ceftriaxone	0.06-2 ≤0.25-8	4	0.5 4	NB
	Ciprofloxacin	0.12->16	0.5	2	87.6
	Meropenem	≤0.03-16	0.12	0.25	NB
	Pip/Tazo	≤1-2	≤1	≤1	NB
	Tigecycline	0.06-0.5	0.12	0.25	100
Methicillin-resistant <i>S. aureus</i> (144)	Omadacycline	≤0.03-2	0.25	0.5	NB
	Ceftriaxone	8-64	>64	>64	NB
	Ciprofloxacin	≤0.06->16	16	>16	28.5
	Meropenem	0.5->32	4	32	NB
	Pip/Tazo	≤1-256	32	128	NB
	Tigecycline Omadacycline	0.06-0.5 ≤0.03-2	0.12 0.25	0.25 0.5	100 NB
Methicillin-susceptible <i>S. epidermidis</i> [#] (72)	Ceftriaxone	≤ 0.25->64	2	0.5 16	NB
	Ciprofloxacin	≤0.06->16	0.25	16	62.5
	Meropenem	≤0.03-16	0.12	8	NB
	Pip/Tazo	≤1-8	≤1	2	NB
	Tigecycline	0.06-0.5	0.12	0.25	NB
Methicillin-resistant <i>S. epidermidis</i> [#] (6)	Omadacycline	≤0.03-2			
	Ceftriaxone	>64			
	Ciprofloxacin	16->16			
	Meropenem	16->32			
	Pip/Tazo	16-64			
	Tigecycline	0.06-0.25			
Penicillin-susceptible ^a S. pneumoniae (107)	Omadacycline	≤0.015-0.12	0.06	0.06	NB
	Ceftriaxone	≤0.12	≤0.12	≤0.12	100
	Ciprofloxacin	≤0.06-8	1	1	NB
	Meropenem Pip/Tazo	≤0.06-0.12 ≤1	≤0.06 ≤1	≤0.06 ≤1	100 NB
	Tigecycline	 ≤0.015-0.12	0.03	0.03	99.1
Penicillin-intermediate ^b <i>S. pneumoniae</i> (24)	Omadacycline	0.03-0.12	0.06	0.12	NB
	Ceftriaxone	≤0.12-1	≤0.12	0.5	100
	Ciprofloxacin	0.5-2	1	2	NB
	Meropenem	≤0.06-0.5	≤0.06	0.5	79.2
	Pip/Tazo	≤1-4	≤1	4	NB
	Tigecycline	≤0.015-0.06	0.03	0.03	100
Penicillin-resistant ^c <i>S. pneumoniae</i> (3)	Omadacycline	0.03-0.12			
	Ceftriaxone Ciprofloxacin	0.5-1 1-2			
	Meropenem	0.5			
	Pip/Tazo	4			
	Tigecycline	≤0.015-0.03			
S. pyogenes (50)	Omadacycline	0.03-0.12	0.06	0.12	NB
	Ceftriaxone	≤0.12	≤0.12	≤0.12	100
	Ciprofloxacin	0.12-2	0.5	0.5	NB
	Meropenem	≤0.06	≤0.06	≤0.06	100
	Pip/Tazo	≤1	≤1	≤1	NB
	Tigecycline	≤0.015-0.12	0.03	0.06	100
S. agalactiae (53)	Omadacycline	0.03-0.25	0.12	0.25	NB
	Ceftriaxone	≤0.12	≤0.12	≤0.12	100
	Ciprofloxacin	0.25->16	0.5	16	NB
	Meropenem Pin/Tazo	≤0.06 ≤1	≤0.06 ≤1	≤0.06 ≤1	100 NB
	Pip/Tazo Tigecycline	≤1 0.03-12	≤1 0.06	≤1 0.06	NВ 100
E. faecalis (93)	Omadacycline	0.06-0.5	0.00	0.00	NB
	Ceftriaxone	1->64	>64	>64	NB
	Ciprofloxacin	0.25->16	1	>16	76.3
	Meropenem	1-16	4	8	NB
	Pip/Tazo	≤1->512	4	4	NB
	Tigecycline	≤0.03-0.25	0.12	0.12	100
E. faecium (43)	Omadacycline	≤0.03-0.25	0.12	0.12	NB
	Ceftriaxone	32->64	>64	>64	NB
	Ciprofloxacin	0.5->16	>16	>16	7
	Meropenem	8->32	>32	>32	NB
	Pip/Tazo	16->512	>512	>512	NB
	Tigecycline	≤0.03-0.12	0.12	0.12	NB

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RESULTS (CONT.)

TABLE 2. Omadacycline in vitro activity against 1573 aerobic Gram-negative bacteriaisolated from patients in Canadian hospitals in 2015

		µg/ml				
Organism and phenotype (no. of isolates)	Antimicrobial Agent	MIC Range	MIC ₅₀	MIC ₉₀	% Susceptib	
<i>E. coli</i> ESBL-negative (489)	Omadacycline	0.5-16	2	4	NB	
	Ceftriaxone	≤0.25->64	≤0.25	≤0.25	98.6	
	Ciprofloxacin	≤0.06->16	≤0.06	>16	81.6	
	Meropenem	≤0.03-0.06	≤0.03	≤0.03	100	
	Pip/Tazo	≤1->512	_0.00 2	4	98.2	
	·					
	Tigecycline	0.12-1	0.25	0.25	100	
<i>E. coli</i> ESBL-positive (69)	Omadacycline	1-16	2	4	NB	
	Ceftriaxone	1->64	64	>64	2.9	
	Ciprofloxacin	≤0.06->16	>16	>16	14.5	
	Meropenem	≤0.03-0.12	≤0.03	0.06	100	
	Pip/Tazo	≤1-256	4	16	94.2	
	Tigecycline	0.12-1	0.25	0.5	100	
<i>K. pneumoniae</i> ESBL-negative (188)	Omadacycline	1->16	2	4	NB	
	Ceftriaxone	≤0.25->64	_ ≤0.25	≤0.25	98.9	
	Ciprofloxacin	≤0.06->16	≤0.06	0.12	95.7	
	Meropenem	≤0.03-8	≤0.03	≤0.03	99.5	
	Pip/Tazo	≤1->512	2	8	98.4	
	Tigecycline	0.25-16	0.5	1	96.8	
K. pneumoniae ESBL-positive (9)	Omadacycline	1-16	2	4	NB	
	Ceftriaxone	≤0.25->64	64	>64	11.1	
	Ciprofloxacin	≤0.06->16	4	>16	22.2	
	Meropenem	≤0.03-8	≤0.03	8	88.9	
	Pip/Tazo	<u> </u>	_0.00 16	>512	66.7	
	Tigecycline	0.5-4	0.5	4	77.8	
K. oxytoca (45)	Omadacycline	1-16	2	4	NB	
	Ceftriaxone	≤0.25->64	≤0.25	1	93.3	
	Ciprofloxacin	≤0.06-0.5	≤0.06	≤0.06	100	
	Meropenem	≤0.03-0.06	≤0.03	≤0.03	100	
	Pip/Tazo	≤1->512	≤1	32	88.9	
	Tigecycline	0.12-4	0.25	0.5	97.8	
E. cloacae (89)	Omadacycline	0.12-16	2	4	NB	
	Ceftriaxone	≤0.25->64	_ ≤0.25	>64	68.5	
	Ciprofloxacin	≤0.06->16	≤0.06	0.12	95.5	
	Meropenem	≤0.03-4	≤0.03	0.12	97.7	
	Pip/Tazo	≤1-256	2	64	85.4	
	Tigecycline	0.12-8	0.5	1	95.1	
P. mirabilis (51)	Omadacycline	16->16	>16	>16	NB	
	Ceftriaxone	≤0.25->64	≤0.25	≤0.25	94.1	
	Ciprofloxacin	≤0.06-16	≤0.06	0.25	92.2	
	Meropenem	≤0.03-0.25	0.06	0.12	100	
	Pip/Tazo	≤1-2	≤1	≤1	100	
	Tigecycline	1-8	4	8	25.5	
$\sum_{n=1}^{\infty} marcocorrection (22)$	Omadacycline	4-16	4	8	NB	
S. marcescens (33)	-					
	Ceftriaxone	≤0.25-0.5	≤0.25	≤0.25	100	
P. aeruginosa (366)	Ciprofloxacin	≤0.06-1	≤0.06	≤0.06	100	
	Meropenem	≤0.03-0.06	0.06	0.06	100	
	Pip/Tazo	≤1-4	≤1	2	100	
	Tigecycline	1-4	1	2	97	
	Omadacycline	2->16	>16	>16	NB	
	Ceftriaxone	≤0.25->64	16	>64	NB	
	Ciprofloxacin	≤0.06->16	0.25	4	79.5	
	Meropenem	≤0.03->32	0.23	8	76.8	
	Pip/Tazo	≤1-512 0.05 × 10	4	32	84.7	
	Tigecycline	0.25->16	16	>16	NB	
S. maltophilia (67)	Omadacycline	2->16	8	16	NB	
	Ceftriaxone	2->64	>64	>64	NB	
	Ciprofloxacin	0.5->16	4	16	NB	
	Meropenem	1->32	>32	>32	NB	
	Pip/Tazo	8->512	256	>512	NB	
			1	4	NB	
	Tigecycline	0.25-8			ND	
A. baumannii (11)	Tigecycline Omadacycline	0.25-8 0.5-1	0.5	1	NB	
A. baumannii (11)	•	0.5-1	0.5 8	1 16	NВ 72.7	
A. baumannii (11)	Omadacycline Ceftriaxone	0.5-1 4-32	8	16	72.7	
A. baumannii (11)	Omadacycline Ceftriaxone Ciprofloxacin	0.5-1 4-32 ≤0.06-0.25	8 0.25	16 0.25	72.7 100	
A. baumannii (11)	Omadacycline Ceftriaxone Ciprofloxacin Meropenem	0.5-1 4-32 ≤0.06-0.25 0.25-1	8 0.25 0.25	16 0.25 1	72.7 100 100	
A. baumannii (11)	Omadacycline Ceftriaxone Ciprofloxacin Meropenem Pip/Tazo	0.5-1 4-32 ≤0.06-0.25 0.25-1 ≤1-16	8 0.25 0.25 ≤1	16 0.25 1 16	72.7 100 100 100	
A. baumannii (11)	Omadacycline Ceftriaxone Ciprofloxacin Meropenem	0.5-1 4-32 ≤0.06-0.25 0.25-1	8 0.25 0.25	16 0.25 1	72.7 100 100	
A. baumannii (11) H. influenzae (156)	Omadacycline Ceftriaxone Ciprofloxacin Meropenem Pip/Tazo	0.5-1 4-32 ≤0.06-0.25 0.25-1 ≤1-16	8 0.25 0.25 ≤1	16 0.25 1 16	72.7 100 100 100	
	Omadacycline Ceftriaxone Ciprofloxacin Meropenem Pip/Tazo Tigecycline	0.5-1 4-32 ≤0.06-0.25 0.25-1 ≤1-16 0.12-0.5	8 0.25 0.25 ≤1 0.25	16 0.25 1 16 0.5	72.7 100 100 100 NB	
	Omadacycline Ceftriaxone Ciprofloxacin Meropenem Pip/Tazo Tigecycline Omadacycline	0.5-1 4-32 ≤0.06-0.25 0.25-1 ≤1-16 0.12-0.5 ≤0.5-2	8 0.25 0.25 ≤1 0.25 0.5	16 0.25 1 16 0.5 1	72.7 100 100 100 NB NB	
	Omadacycline Ceftriaxone Ciprofloxacin Meropenem Pip/Tazo Tigecycline Omadacycline Ceftriaxone Ciprofloxacin	0.5-1 4-32 ≤0.06-0.25 0.25-1 ≤1-16 0.12-0.5 ≤0.5-2 ≤0.06-2	8 0.25 0.25 ≤1 0.25 0.5 ≤0.06	16 0.25 1 16 0.5 1 ≤0.06	72.7 100 100 100 NB NB 100	
	Omadacycline Ceftriaxone Ciprofloxacin Meropenem Pip/Tazo Tigecycline Omadacycline Ceftriaxone	0.5-1 4-32 ≤0.06-0.25 0.25-1 ≤1-16 0.12-0.5 ≤0.5-2 ≤0.06-2 ≤0.015-0.06	8 0.25 0.25 ≤1 0.25 0.5 ≤0.06 ≤0.015	16 0.25 1 16 0.5 1 ≤0.06 ≤0.015	72.7 100 100 100 NB NB 100 100	

NB – no CLSI breakpoints defined ESBL - extended spectrum ß-lactamase