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 (≤17/18-64/≥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; www.can-r.ca) (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.

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 100 µl/well of cation adjusted Mueller-Hinton broth and inoculated to achieve a final concentration of approximately 5 x 10^5 CFU/ml 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, methicillin-resistant *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 Gram-negative pathogens.

REFERENCES

1. Macone et al. *In vitro* and *in vivo* antibacterial activities of omadacycline a novel aminomethylcycline. Antimicrob Agents Chemother 2014;58:1127-1135.
2. Tanaka et al. Discovery pharmacology and clinical profileof omadacycline a novel aminomethylcycline antibiotic. Biorg Med Chem 2016;24:6409-6419.
3. Villano et al. Omadacycline: development of a novel aminomethylcycline antibiotic for treating drug-resistant bacterial infections. Future Microbiol 2016;11:1421-1434.
4. Sun at al. Randomized open label study of the pharmacokinetics and safety of oral and intravenous administration of omadacycline to healthy subjects. Antimicrob Agents Chemother 2016;60:7431-7435.
5. Pfaller et al. Surveillance of omadacycline activity against clinical isolates from the global collection (North America, Europe, Latin America, Asia-Western Pacific) 2010-2011. Antimicrob Agents Chemother 2017;61:1-7.
6. Zhanel et al. Antimicrobial susceptibility of 22,746 pathogens from Canadian hospitals: Results of the CANWARD 2007-2011 study. Journal of Antimicrobial Chemotherapy 2013;68 (Suppl 1):7-22.

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RESULTS

TABLE 1. Omadacycline *in vitro* activity against 1199 aerobic Gram-positive bacteria isolated from patients in Canadian hospitals in 2015

Organism and phenotype (no. of isolates)	Antimicrobial Agent	µg/ml MIC Range	µg/ml MIC_{50}	µg/ml MIC_{90}	% Susceptible
Methicillin-susceptible *S. aureus* (604)	**Omadacycline**	**0.06-2**	**0.25**	**0.5**	**NB**
	Ceftriaxone	≤0.25-8	4	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 *S. aureus* (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	0.06-0.5	0.12	0.25	100
Methicillin-susceptible *S. epidermidis*[a] (72)	**Omadacycline**	**≤0.03-2**	**0.25**	**0.5**	**NB**
	Ceftriaxone	≤0.25->64	2	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 *S. epidermidis*[a] (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	≤0.06-0.12	≤0.06	≤0.06	100
	Pip/Tazo	≤1	≤1	≤1	NB
	Tigecycline	≤0.015-0.12	0.03	0.03	99.1
Penicillin-intermediate[b] *S. pneumoniae* (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] *S. pneumoniae* (3)	**Omadacycline**	**0.03-0.12**			
	Ceftriaxone	0.5-1			
	Ciprofloxacin	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	≤0.06	≤0.06	≤0.06	100
	Pip/Tazo	≤1	≤1	≤1	NB
	Tigecycline	0.03-12	0.06	0.06	100
E. faecalis (93)	**Omadacycline**	**0.06-0.5**	**0.12**	**0.25**	**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

NB – no CLSI breakpoints defined
[a] Methicillin-susceptible: ceftazolin MIC ≤8 µg/ml; methicillin-resistant: ceftazolin MIC ≥32 µg/ml
[a] Penicillin-susceptible, MIC ≤0.06 µg/ml.
[b] Penicillin-intermediate, MIC 0.12-1 µg/ml.
[c] Penicillin-resistant, MIC ≥2 µg/ml.

RESULTS (CONT.)

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

Organism and phenotype (no. of isolates)	Antimicrobial Agent	µg/ml MIC Range	µg/ml MIC_{50}	µg/ml MIC_{90}	% Susceptible
E. coli 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	2	4	98.2
	Tigecycline	0.12-1	0.25	0.25	100
E. coli 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
K. pneumoniae 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	2->512	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
S. marcescens (33)	**Omadacycline**	**4-16**	**4**	**8**	**NB**
	Ceftriaxone	≤0.25-0.5	≤0.25	≤0.25	100
	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
P. aeruginosa (366)	**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	0.5	8	76.8
	Pip/Tazo	≤1->512	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
	Tigecycline	0.25-8	1	4	NB
A. baumannii (11)	**Omadacycline**	**0.5-1**	**0.5**	**1**	**NB**
	Ceftriaxone	4-32	8	16	72.7
	Ciprofloxacin	≤0.06-0.25	0.25	0.25	100
	Meropenem	0.25-1	0.25	1	100
	Pip/Tazo	≤1-16	≤1	16	100
	Tigecycline	0.12-0.5	0.25	0.5	NB
H. influenzae (156)	**Omadacycline**	**≤0.5-2**	**0.5**	**1**	**NB**
	Ceftriaxone	≤0.06-2	≤0.06	≤0.06	100
	Ciprofloxacin	≤0.015-0.06	≤0.015	≤0.015	100
	Meropenem	≤0.06-0.25	≤0.06	0.12	100
	Pip/Tazo	≤1-2	≤1	≤1	99.4
	Tigecycline	0.12-0.5	0.5	1	NB

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