Activity of Omadacycline Against Clinical Isolates of *Neisseria gonorrhoeae*, Including Ciprofloxacin-Resistant Isolates

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ABSTRACT

Background: The prevalence and ease of transmission of gonococcal infection coupled with the high degree of resistance among *N. gonorrhoeae* (GC) to former front-line therapies (penicillin, tetracycline, and ciprofloxacin) and recent emergence of cephalosporin resistance has caused concern about gonorrhea control going forward. Omadacycline (OMC), a new once daily oral and intravenous aminomethylcycline currently in phase 3 development for the treatment of skin and respiratory infections, retains potent in vitro activity against bacteria resistant to legacy tetracyclines. In this study, the in vitro activity of OMC against recent clinical isolates of GC including ciprofloxacin-resistant (CIP-R) isolates was evaluated.

Methods: MICs of OMC, CIP, and ceftriaxone (CRO) were determined by agar dilution in accordance with CLSI guidelines (CLSI M7 and M100) against 52 clinical isolates of GC, 24 of which were CIP-R. In addition, the impact of testing susceptibility by agar dilution relative to broth microdilution using GC medium was evaluated using concurrent inocula of *N. gonorrhoeae* ATCC 49226.

Results: The activity (µg/mL) of OMC and comparators against GC is shown in the table below.

Test	Overall (n=52)		CIP-S (n=28)		CIP-R (n=24)	
Agent	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$	MIC range	$MIC_{50/90}$
OMC	0.25 – 4	2/4	0.25 – 2	1/2	1 – 4	4/4
CIP	0.002 – >8	0.008/>8	0.002 – 0.015	0.004/0.008	2 – >8	>8/>8
CRO	0.002 – 0.12	0.008/0.06	0.002 – 0.015	0.004/0.008	0.004 – 0.12	0.03/0.06

OMC had an overall $MIC_{50/90}$ of 2/4 µg/mL and maintained activity against CIP-R GC with an MIC90 within 2-fold that observed for CIP-S GC. CRO also maintained activity against CIP-R GC, though the MIC_{90} was reduced 8-fold relative to CIP-S GC. The OMC agar dilution MIC against *N. gonorrhoeae* ATCC 49226 (2 µg/mL) was 4-fold higher than the OMC broth microdilution MIC (0.5 µg/mL).

Conclusions: OMC exhibited in vitro activity against the evaluated GC isolates and maintained potency against CIP-R isolates which are commonly encountered clinically. The variation in potency of OMC against GC by broth microdilution relative to agar dilution suggests variability in activity by test method.

BACKGROUND

- Gonorrhea is the second most commonly reported communicable disease, with 820,000 *N. gonorrhoeae* infections per year in the US alone[1-2].
- Guidelines from the CDC for the antibiotic treatment of gonorrhea have evolved over the past decade due to changes in antibiotic resistance:
  - Resistance to fluoroquinolones prompted the CDC in 2007 to remove these agents from the list of recommended antibiotics for the treatment of gonorrhea in the US[3].
  - In 2010 the CDC removed oral cephalosporins from the list of agents recommended for treating gonorrhea due to increasing cefixime MICs[4].
- Combination therapy with ceftriaxone and azithromycin is currently the only treatment recommended by the CDC for gonorrhea[5].
- The recent emergence of *N. gonorrhoeae* with reduced susceptibility to ceftriaxone[6-8] coupled with the overall ease of transmission has caused significant concern about gonorrhea control going forward and highlights the need for new agents.
- Omadacycline, a new once daily oral and IV aminomethylcycline in phase 3 development for the treatment of skin and respiratory infections, maintains potent activity against bacteria resistant to legacy tetracyclines.

OBJECTIVE

To evaluate the in vitro activity of omadacycline against recent clinical isolates of *N. gonorrhoeae*, including isolates with resistance to fluoroquinolones.

METHODS

- Test isolates of *N. gonorrhoeae* for MIC testing included quality control strain ATCC 49226 from the American Type Culture Collection (ATCC, Manassas, VA) and 52 clinical isolates collected from 2012-2014 at the State of Michigan Public Health Department (Lansing, MI; n=23) and Public Health Laboratory in Ontario, Canada (n=29).
- Isolates resistant to ciprofloxacin were preferentially selected for analysis.
- MICs were determined by agar dilution in accordance with Clinical and Laboratory Standards Institute (CLSI) guideline M7-A10[9] and M100-S25[10] using supplemented GC agar.
- In addition, triplicate independent inocula of *N. gonorrhoeae* ATCC 49226 were evaluated concurrently by agar dilution and by broth microdilution (using GC broth) to evaluate potential variability in activity by these two methods.

RESULTS

- Overall, omadacycline had an $MIC_{50/90}$ of 2/4 µg/mL against the evaluated isolates, 46.2% (24/28) of which were ciprofloxacin-resistant (CIP-R; **Table 1; Figure 1**).
- Omadacycline maintained potent activity against CIP-R isolates with an $MIC_{50/90}$ of 4/4 µg/mL relative to the 1/2 µg/mL observed against CIP-S isolates (**Table 1**).
- A 2-fold increase in omadacycline MICs against CIP-R relative to CIP-S isolates was apparent by MIC distribution (**Figure 1**).
- Ceftriaxone had potent activity against N. gonorrhoeae overall with an $MIC_{50/90}$ of 0.008/0.06 µg/mL (**Table 1; Figure 2**).
- In contrast to omadacycline, the $MIC_{50/90}$ of ceftriaxone was 8-fold higher against CIP-R isolates (0.03/0.06 µg/mL) relative to CIP-S isolates (0.004/0.008 µg/mL; **Table 1**).
- This 8-fold difference in ceftriaxone activity against CIP-S and CIP-R isolates was also apparent by MIC distribution (**Figure 2**).
- As expected given the high degree of ciprofloxacin-resistant isolates selected for evaluation, ciprofloxacin only displayed potent activity against CIP-S isolates ($MIC_{50/90}$ = 0.004/0.008 µg/mL; **Table 1, Figure 3**).
- Based on concurrent testing against ATCC 49266, broth microdilution MICs of omadacycline, tigecycline, and ciprofloxacin were 4-fold lower than agar dilution MICs (**Table 2**).

RESULTS

Table 1. Summary of the Activity of Omadacycline, Ciprofloxacin, and Ceftriaxone Against *N. gonorrhoeae*

Overall (n=52)			
Drug	MIC range	MIC_{50}	MIC_{90}
Omadacycline	0.25 - 4	2	4
Ciprofloxacin	0.002 - >8	0.008	>8
Ceftriaxone	0.002 - 0.12	0.008	0.06
CIP-S (n=28)			
Drug	MIC range	MIC_{50}	MIC_{90}
Omadacycline	0.25 - 2	1	2
Ciprofloxacin	0.002 - 0.015	0.004	0.008
Ceftriaxone	0.002 - 0.015	0.004	0.008
CIP-R (n=24)			
Drug	MIC range	MIC_{50}	MIC_{90}
Omadacycline	1 - 4	4	4
Ciprofloxacin	2 - >8	>8	>8
Ceftriaxone	0.004 - 0.12	0.03	0.06

Table 2. Summary of the Activity of Omadacycline, Ciprofloxacin, and Ceftriaxone Against Quality Control Isolate *N. gonorrhoeae* ATCC 49266 During Testing

Agar MIC as Observed during Routine QC Testing

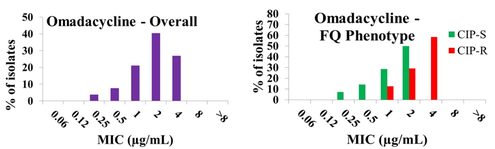
MIC (µg/mL)		
Omadacycline	Ciprofloxacin	Ceftriaxone
1-2	0.002 - 0.008 (0.001-0.008)[1]	0.004 - 0.008 (0.004-0.015)[1]

MIC as Observed during Concurrent Testing of Triplicate Independent Inocula by Broth Microdilution and Agar Dilution

GC Agar MIC (µg/mL)		
Omadacycline	Ciprofloxacin	Tigecycline
2	0.008 (0.001-0.008)[1]	0.25
GC Broth MIC (µg/mL)		
Omadacycline	Ciprofloxacin	Tigecycline
0.5	0.002	0.06

[1] CLSI QC range shown in parenthesis

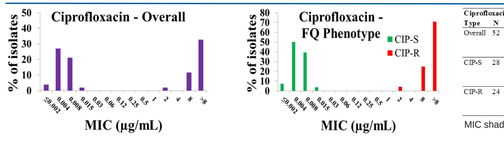
Figure 1. MIC Distribution of Omadacycline Against Clinical *N. gonorrhoeae* Overall and by Ciprofloxacin Phenotype



Omadacycline Type	N		MIC (µg/mL) 0.06	0.12	0.3	0.5	1	2	4	8	>8
Overall	52	n			2	4	11	21	14		
		%			3.8	7.7	21.2	40.4	26.9		
		cum %			3.8	11.5	32.7	73.1	100		
CIP-S	28	n			2	4	8	14			
		%			7.1	14.3	28.6	50.0			
		cum %			7.1	21.4	50.0	100			
CIP-R	24	n					3	7	14		
		%					12.5	29.2	58.3		
		cum %					12.5	41.7	100		

MIC shaded in green = MIC_{50}; MIC shaded in orange = MIC_{90}

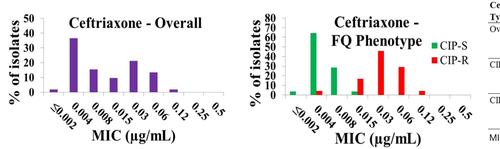
Figure 2. MIC Distribution of Ciprofloxacin Against Clinical *N. gonorrhoeae* Overall and by Ciprofloxacin Phenotype



Ciprofloxacin Type	N		MIC (µg/mL) ≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	>8
Overall	52	n	2	14	11	1									6	17
		%	3.8	26.9	21.2	1.9							1.9		11.5	32.7
		cum %	3.8	30.8	51.9	53.8							55.8		67.3	100
CIP-S	28	n	2	14	11	1										
		%	7.1	50.0	39.3	3.6										
		cum %	7.1	57.1	96.4	100										
CIP-R	24	n										1		6	17	
		%										4.2		25.0	70.8	
		cum %										4.2		29.2	100	

MIC shaded in green = MIC_{50}; MIC shaded in orange = MIC_{90}

Figure 3. MIC Distribution of Ceftriaxone Against Clinical *N. gonorrhoeae* Overall and by Ciprofloxacin Phenotype



Ceftriaxone Type	N		MIC (µg/mL) ≤0.002	0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5
Overall	52	n	1	19	8	5	11	7	1		
		%	1.9	36.5	15.4	9.6	21.2	13.5	1.9		
		cum %	1.9	38.5	53.8	63.5	84.6	98.1	100		
CIP-S	28	n	1	18	8	1					
		%	3.6	64.3	28.6	3.6					
		cum %	3.6	67.9	96.4	100					
CIP-R	24	n		1		4	11	7	1		
		%		4.2		16.7	45.8	29.2	4.2		
		cum %		4.2		20.8	66.7	95.8	100		

MIC shaded in green = MIC_{50}; MIC shaded in orange = MIC_{90}

CONCLUSIONS

- Omadacycline was active against recent clinical isolates of *N. gonorrhoeae* and maintained activity against CIP-R isolates, which are commonly encountered clinically.
- Despite the potent activity observed for ceftriaxone across the evaluated isolates of *N. gonorrhoeae*, the activity observed against CIP-R isolates was reduced compared to that observed with CIP-S isolates, suggesting some degree of co-resistance between these classes.
- The variation in potency of omadacycline and other agents by broth microdilution relative to agar dilution suggests variation in activity of these agents by test method. Currently agar dilution is the accepted standard method for susceptibility testing for *N. gonorrhoeae*.
- The overall activity profile of omadacycline as observed in this study suggests that omadacycline may be useful in the fight against resistant *N. gonorrhoeae* going forward.

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