IDWEEK 2024
Poster #1528

In vitro activity of omadacycline and comparator agents against a collection of *Neisseria gonorrhoeae* urine isolates collected from the United States during 2018-2020

S.J. Ryan Arends[1], J.V. Pierce[2], H. Becker[1], M. Caron[2], J. Lindley[1], A. W. Serio[2], M. Castanheira[1]

[1]Element Iowa City (JMI Laboratories), North Liberty, Iowa, USA [2]Paratek Pharmaceuticals, King of Prussia, Pennsylvania, USA

Introduction

Omadacycline is a third-generation tetracycline class antibacterial approved for treatment of adults with acute bacterial skin and skin structure infections and community-acquired bacterial pneumonia caused by indicated organisms and is available in both iv and oral formulations.

Omadacycline is active against bacterial isolates expressing the most common tetracycline resistance mechanisms. Additionally, omadacycline is highly active against two of the most common sexually transmitted pathogens, *Mycoplasma genitalium* and *Chlamydia trachomatis*.

Drug resistant *Neisseria gonorrhoeae* is an urgent threat pathogen, with resistance to all but one class of antibiotics and half of all infections resistant to at least one antibiotic.

Doxycycline, an older tetracycline class drug, is currently being used for STI prophylaxis among high-risk populations, demonstrating a 55% reduction in *Neisseria* infections (Vanbaelen et al. 2024). However, tetracycline class resistance rates range from 10-90% by country and increased use of doxycycline may increase resistance rates in the US.

In this study, the *in vitro* activity of omadacycline and comparator agents was evaluated against a contemporary collection of *N. gonorrhoeae* clinical isolates.

In addition, analysis of publicly available genomic sequences for these isolates was performed to determine the molecular mechanisms of tetracycline resistance including, among others, chromosomal mutations in the *mtrR* (efflux pump), *porB* (porin), *rpsJ* (target site mutation in 30S ribosome) genes, and the acquisition of the *tet*(M) ribosomal protection protein.

Materials and Methods

100 *N. gonorrhoeae* clinical isolates collected as part of the Gonococcal Isolate Surveillance Project (GISP) were procured from BEI Resources.

Isolates were collected throughout the United States between 2018-2020 from the urethra of patients with urethritis.

Bacterial species were confirmed by JMI Laboratories using standard microbiology methods and matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Daltonics, Bremen, Germany).

Susceptibility of omadacycline and comparator agents was determined using agar dilution methodology per Clinical and Laboratory Standards Institute (CLSI) guidelines.

- The testing medium was GC medium base (BD Difco) with 1% defined growth supplement (BD BBL IsovitaleX Enrichment).
- The modal minimal inhibitory concentration (MIC) of omadacycline and comparator agents were determined in triplicate by agar dilution testing.

Resistant or non-susceptible phenotypes were interpreted using breakpoints published by CLSI (2024).

For isolates where sequencing data was available (n=95), acquired resistance genes *tet*(M) or chromosomal mutations in *rpsJ*, *mtrR*, or *porB* were identified from genome sequences using ResFinder 4.0.

Results

Omadacycline displayed activity ($MIC_{50/90}$, 2/4 µg/mL) against *N. gonorrhoeae* isolates and all omadacycline MIC values observed were ≤8 µg/mL (Table 1).

Many isolates had limited susceptibility to comparator agents including tetracycline (13% S), ciprofloxacin (60% S), or penicillin (4% S), while most were susceptible azithromycin (93% S), cefixime (99% S), and ceftriaxone (99% S) (Table 1).

Table 1 Antimicrobial activity of omadacycline and comparators tested against 100 *N. gonorrhoeae* isolates

Antimicrobial agent	µg/mL			CLSI[a]		
	MIC_{50}	MIC_{90}	Range	%S	%I	%R
Omadacycline	2	4	0.12 to 8			
Tetracycline	1	2	≤0.12 to >64	13	65	22
Penicillin	0.5	4	0.06 to >4	4	80	16
Ciprofloxacin	0.015	>1	≤0.002 to >1	60	1	39
Azithromycin	0.25	1	≤0.03 to >4	93	-	7
Cefixime	0.015	0.03	≤0.004 to >2	99	-	1
Ceftriaxone	0.008	0.03	≤0.002 to 1	99	-	1

[a] Criteria as published by CLSI (2024).

Among isolate subsets with non-susceptible or resistance phenotypes to comparator agents, omadacycline $MIC_{50/90}$ remained within 1 doubling dilution of those observed for all isolates tested ($MIC_{50/90}$, 2/4 µg/mL, Table 2).

The omadacycline $MIC_{50/90}$ was 4-fold higher among tetracycline-resistant isolates ($MIC_{50/90}$, 2/8 µg/mL) compared to tetracycline susceptible isolates ($MIC_{50/90}$, 0.5/2 µg/mL)

Table 2 Cumulative distribution of omadacycline MIC values tested against comparator-resistant or non-susceptible *N. gonorrhoeae* subsets

Resistant subset (No. isolates)	No. of isolates and cumulative % inhibited at omadacycline MIC (µg/mL) of:								MIC_{50}	MIC_{90}
	0.06	0.12	0.25	0.5	1	2	4	8		
All Isolates (100)	0 0.0	1 1.0	6 7.0	9 16.0	27 43.0	37 80.0	12 92.0	8 100.0	2	4
Azithromycin-NS (7)					0 0.0	3 42.9	2 71.4	2 100.0	4	
Cefixime-NS (1)					0 0.0	1 100.0			2	
Ceftriaxone-NS (1)					0 0.0	1 100.0			2	
Ciprofloxacin-R (39)			0 0.0	2 5.1	13 38.5	18 84.6	5 97.4	1 100.0	2	4
Penicillin-R (16)				0 0.0	5 31.3	8 81.3	3 100.0		2	4
Tetracycline-S (13)	0 0.0	1 7.7	5 46.2	4 76.9	1 84.6	2 100.0			0.5	2
Tetracycline-I (65)		0 0.0	1 1.5	4 7.7	22 41.5	29 86.2	9 100.0		2	4
Tetracycline-R (22)			0 0.0	1 4.5	4 22.7	6 50.0	3 63.6	8 100.0	2	8
Tetracycline-NS (87)		0 0.0	1 1.1	5 6.9	26 36.8	35 77.0	12 90.8	8 100.0	2	4

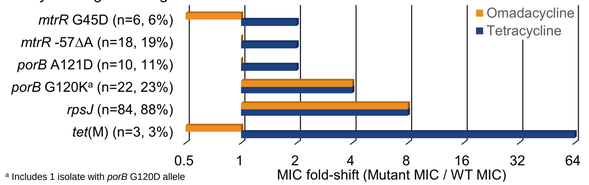
I, Intermediate; NS, non-susceptible (includes intermediate and resistant); R, resistant; S, susceptible per CLSI breakpoints.

The *rpsJ* mutation was widespread among isolates (88% of all *N. gonorrhoeae* isolates), including those with additional mutations in *porB* (23%), the *mtrR* promoter (25%) and *tet*(M) (3%, Figure 1).

Omadacycline displayed MIC values ≤1 µg/mL among isolates (n=3) with high level tetracycline resistance (MIC ≥16 µg/mL), all of which were found to have the *tet(M)* gene, which increased the tetracycline MIC to 32 µg/mL. Additionally, all isolates with *tet*(M) also had the *rpsJ* mutation.

Isolates with the *mtrR* promoter G45D mutation and the -57ΔA mutation genotypes increased the tetracycline MIC 256-fold and 4-fold, respectively, while omadacycline MIC values were not affected.

Figure 1 Effect of tetracycline resistance alleles on activity of omadacycline and tetracycline against *N. gonorrhoeae* isolates



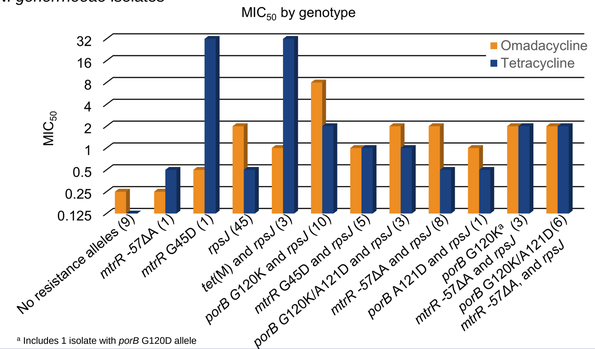
[a] Includes 1 isolate with *porB* G120D allele

The omadacycline $MIC_{50/90}$ increased 8-fold for isolates with the *rpsJ* mutation ($MIC_{50/90}$, 2/4 µg/mL) compared to isolates with wild-type *rpsJ* ($MIC_{50/90}$, 0.25/0.5 µg/mL).

Tetracycline activity was affected similarly with the $MIC_{50/90}$ increasing 4- to ≥8-fold (WT $MIC_{50/90}$ ≤0.12/0.5 µg/mL vs *rpsJ* $MIC_{50/90}$, 1/2 µg/mL) (Figure 2).

The omadacycline MIC_{50} increased another 2- to 4-fold when *rpsJ* and *porB* G120K mutations were combined (MIC_{50}, 8 µg/mL; Figure 2) while tetracycline MICs were unaffected by the addition of the *porB* G120K mutation to the *rspJ* V57M mutation.

Figure 2 MIC_{50} values of omadacycline and tetracycline for various genotypes of *N. gonorrhoeae* isolates



[a] Includes 1 isolate with *porB* G120D allele

Conclusions

Omadacycline MIC values ranged from 0.12-8 µg/mL against a set of recent *N. gonorrhoeae* clinical isolates.

Omadacycline MIC distributions were minimally impacted by isolates non-susceptible or resistant to azithromycin, cefixime, ceftriaxone, ciprofloxacin, or penicillin, although some of these subsets had very low numbers.

Omadacycline MICs were unaffected by the presence of *tet*(M), a driver of high-level resistance to both tetracycline and doxycycline, as well as *mtrR*-promoter mutations, but had elevated MICs in the presence of both the *porB* and *rpsJ* mutations.

Based on this data, doxycycline would likely no longer be an effective option for prophylaxis or treatment in regions where *tet*(M) carriage is high, while omadacycline would be expected to retain activity.

These results support the further research of omadacycline as a potential treatment for *N. gonorrhoeae* infections, especially for those with high level tetracycline resistance.

References

CLSI. 2018. M07Ed11. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 11th Edition. Clinical and Laboratory Standards Institute, Wayne, PA.

CLSI. 2024. M100Ed34E. Performance standards for antimicrobial susceptibility testing: 34th Edition. Clinical and Laboratory Standards Institute, Wayne, PA.

Vanbaelen et al. 45 years of tetracycline post exposure prophylaxis for STIs and the risk of tetracycline resistance: a systematic review and meta-analysis BMC Infectious Diseases (2024) 24:376

Acknowledgements

This project has been funded in whole or in part with Federal funds from the National Institutes of Health, Department of Health and Human Services under Contract No. 75N93019D00011 / 75N93023F00003. The content of this publication does not necessarily reflect the views or policies of the Department of Health and Human Services, nor does mention of trade names, commercial products, or organizations imply endorsement by the U.S. Government.

Disclosures

A.W. Serio and J.V. Pierce are employees of Paratek Pharmaceuticals, Inc.

Contact

S.J. Ryan Arends, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Email: ryan.arends@element.com

SCAN ME