ID Week 2018
Poster #1377

Omadacycline *In Vitro* Activity against a Molecularly Characterized Collection of Clinical Isolates with Known Tetracycline Resistance Mechanisms

RE MENDES[1], M CASTANHEIRA[2], ES ARMSTRONG[2], JN STEENBERGEN[2], RK FLAMM[1]

[1]JMI Laboratories, North Liberty, Iowa, USA; [2] Paratek Pharmaceuticals, King of Prussia, Pennsylvania, USA

Contact Information:
Rodrigo E. Mendes, PhD
JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, IA 52317
Phone: (319) 665-3370
Fax: (319) 665-3371
Email: rodrigo-mendes@jmilabs.com

To obtain a PDF of this poster:
- Scan the QR code
- Visit https://paratekpharma.com/media/1585/idweek-2018-1377-activity-tet-resistant-collection.pdf

Charges may apply.
No personal information is stored.

Introduction

- The tetracycline class of antibiotics have been in clinical use for approximately 70 years and have a well-described safety and tolerability profile
- Omadacycline is an investigational aminomethylcycline agent related to tetracycline, with modifications in its chemical structure to overcome the main tetracycline resistance mechanisms, such as efflux pumps and ribosomal protection
- This investigational aminomethylcycline demonstrates potent *in vitro* activity against common gram-positive aerobes (including methicillin- and penicillin-resistant strains), many gram-negative aerobes, anaerobes, and atypical bacterial pathogens
- This study evaluated the *in vitro* activity of omadacycline against a broad collection of clinical isolates with molecularly characterized tetracycline resistance mechanisms

Materials and Methods

Bacterial organisms

- A total of 167 gram-positive and -negative isolates from the worldwide SENTRY Antimicrobial Surveillance Program were included in this study, and the vast majority (79%) of isolates were from the 2016 sampling year
- A global collection of tetracycline-susceptible gram-positive and -negative (2016) isolates were selected as control groups and showed the following MIC results:
  - Gram-positive: omadacycline ($MIC_{50/90}$, 0.12/0.25 µg/mL), tetracycline ($MIC_{50/90}$, ≤0.5/≤0.5 µg/mL), doxycycline ($MIC_{50/90}$, ≤0.06/0.12 µg/mL), and tigecycline ($MIC_{50/90}$, 0.06/0.12 µg/mL)
  - Gram-negative: omadacycline ($MIC_{50/90}$, 1/2 µg/mL), tetracycline ($MIC_{50/90}$, 1/2 µg/mL), doxycycline ($MIC_{50/90}$, 1/2 µg/mL), and tigecycline ($MIC_{50/90}$, 0.25/0.5 µg/mL)

Antimicrobial susceptibility testing

- Selected isolates were tested for antimicrobial susceptibility using broth microdilution panels manufactured by JMI Laboratories (North Liberty, Iowa, USA) per the Clinical and Laboratory Standards Institute (CLSI)
- MIC values obtained against clinical isolates were interpreted using published CLSI (M100, 2017) and European Committee on Antimicrobial Susceptibility Testing (EUCAST; 2017) breakpoints, when available

Characterizing tetracycline resistance mechanisms

- Bacterial genomes were sequenced on a MiSeq Sequencer (JMI Laboratories)
- FASTQ format sequencing files for each sample set were assembled screened against known tetracycline resistance determinants

Table 1 Activity of omadacycline and comparator agents when tested against tetracycline-resistant gram-positive isolates

Genotype (no. tested) / Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI %I	CLSI %R	EUCAST[a] %S	EUCAST %I	EUCAST %R
tet(K) (14)[b]									
Omadacycline	0.12	0.25	0.03 — 0.25						
Tetracycline	4	>8	2 — >8	78.6	0.0	21.4	0.0	7.1	92.9
Doxycycline	0.5	0.5	0.25 — 0.5	100.0	0.0	0.0	100.0	0.0	0.0
Tigecycline[c]	0.06	0.25	≤0.03 — 0.25	100.0			100.0		0.0
tet(L) and *tet*(M) (10)[d]									
Omadacycline	0.12	0.25	0.12 — 0.25						
Tetracycline	>8	>8	>8	0.0	0.0	100.0			
Doxycycline	>8	>8	>8	0.0	0.0	100.0			
Tigecycline	0.06	0.12	0.06 — 0.25	100.0			100.0	0.0	0.0
tet(M) (16)[e]									
Omadacycline	0.06	2	0.03 — 4						
Tetracycline	2	>8	0.5 — >8	50.0	18.8	31.2			
Doxycycline	0.5	8	0.5 — 8	46.7	40.0	13.3			
Tigecycline	≤0.03	1	≤0.03 — 1	87.5					

[a] Criteria as published by CLSI 2017 and EUCAST 2017.
[b] Results obtained against 14 *Staphylococcus aureus* isolates.
[c] Breakpoints from FDA Package Insert revised 12/2014.
[d] Results obtained against 6 *Enterococcus faecalis* and 4 *S. aureus* isolates.
[e] Results obtained against 2 *E faecalis*, 4 *S. aureus*, 2 *Streptococcus agalactiae*, 7 *S. pneumoniae*, and 1 *S. sanguinis* isolates.

Table 2 Activity of omadacycline and comparator antimicrobial agents when tested against tetracycline-resistant *Enterobacteriaceae* isolates

Genotype (no. tested) / Antimicrobial agent	MIC_{50}	MIC_{90}	Range	CLSI[a] %S	CLSI %I	CLSI %R	EUCAST[a] %S	EUCAST %I	EUCAST %R
tet(A) (32)[b]									
Omadacycline	4	16	0.5 — >32						
Tetracycline	>16	>16	1 — >16	6.2	0.0	93.8			
Doxycycline	>8	>8	0.5 — >8	21.9	15.6	62.5			
Tigecycline[c]	0.5	2	≤0.06 — 4	96.9	3.1	0.0	84.4	12.5	3.1
tet(A) and *tet*(D) (18)[d]									
Omadacycline	4	32	1 — 32						
Tetracycline	>16	>16	>16	0.0	0.0	100.0			
Doxycycline	>8	>8	>8	0.0	0.0	100.0			
Tigecycline	0.5	2	0.12 — 4	94.4	5.6	0.0	83.3	11.1	5.6
tet(B) (25)[e]									
Omadacycline	1	4	0.5 — 4						
Tetracycline	>16	>16	16 — >16	0.0	0.0	100.0			
Doxycycline	>8	>8	8 — >8	0.0	8.0	92.0			
Tigecycline	0.25	0.5	0.12 — 1	100.0	0.0	0.0	100.0	0.0	0.0
tet(D) (37)[f]									
Omadacycline	2	8	0.5 — 16						
Tetracycline	>16	>16	>16	0.0	0.0	100.0			
Doxycycline	>8	>8	2 — >8	2.7	0.0	97.3			
Tigecycline	0.5	1	0.12 — 4	97.3	2.7	0.0	94.6	2.7	2.7
Other *tet* genes (15)[g]									
Omadacycline	2	8	0.25 — 32						
Tetracycline	>16	>16	1 — >16	6.7	0.0	93.3			
Doxycycline	>8	>8	1 — >8	20.0	0.0	80.0			
Tigecycline	0.5	2	≤0.06 — 2	100.0	0.0	0.0	80.0	20.0	0.0

[a] Criteria as published by CLSI 2017 and EUCAST 2017.
[b] Results obtained against 1 *Citrobacter freundii*, 4 *Enterobacter aerogenes*, 1 *E. cloacae*, 13 *Escherichia coli*, 3 *Klebsiella oxytoca*, 10 *K. pneumoniae* isolates.
[c] Breakpoints from FDA Package Insert revised 12/2014.
[d] Results obtained against 4 *E. coli*, 1 *K. oxytoca*, 13 *K. pneumoniae* isolates.
[e] Results obtained against 4 *C. freundii*, 1 *E. cloacae*, 10 *E. coli*, 5 *K. oxytoca*, 5 *K. pneumoniae* isolates.
[f] Results obtained against 6 *C. freundii*, 13 *E. cloacae*, 4 *E. coli*, 4 *K. oxytoca*, 10 *K. pneumoniae* isolates.
[g] Results obtained against 5 *E. coli* and 2 *K. pneumoniae* isolates carrying *tet*(A) + *tet*(B); 1 *E. coli* isolate carrying *tet*(B) + *tet*(C); 1 *E. coli* isolate carrying *tet*(B) + *tet*(D); 1 *C. freundii* isolate and 1 *E. cloacae* isolate carrying *tet*(C); 1 *E. cloacae* isolate, 2 *K. pneumoniae* isolates, and 1 *E. coli* isolate carrying *tet*(W).

Results

- Activity of omadacycline against tetracycline-resistant gram-positive isolates (Table 1 and Figure 1)
  - Omadacycline ($MIC_{50/90}$, 0.12/0.25 µg/mL) and tigecycline ($MIC_{50/90}$, 0.06/0.25 µg/mL) showed similar MIC results when tested against *Staphylococcus aureus* carrying *tet*(K)
  - Omadacycline (MIC_{90}, 0.25–2 µg/mL) and tigecycline (MIC_{90}, 0.12–1 µg/mL) showed potent MIC results against gram-positive isolates carrying *tet*(L) and/or *tet*(M)
  - Tetracycline and doxycycline had MIC_{50} values of ≥8 µg/mL against isolates carrying *tet* genes, except for doxycycline ($MIC_{50/90}$, 0.5/0.5 µg/mL) that was active against those carrying *tet*(K) genes
- Activity of omadacycline against tetracycline-resistant gram-negative isolates (Table 2 and Figure 2)
  - Omadacycline ($MIC_{50/90}$, 1/4 µg/mL) and tigecycline ($MIC_{50/90}$, 0.25/0.5 µg/mL) had the lowest MIC results against gram-negative *Enterobacteriaceae* isolates carrying *tet*(B)
  - Omadacycline showed MIC_{50} results of 2, 4, and 4 µg/mL, respectively, against isolates carrying *tet*(D), *tet*(A) and *tet*(A)+*tet*(D)
  - Among tetracyclines, omadacycline ($MIC_{50/90}$, 2/8 µg/mL) and tigecycline ($MIC_{50/90}$, 0.5/2 µg/mL) demonstrated the lowest MIC results when tested against gram-negative isolates harboring a combination of other *tet* genes
  - Tetracycline and doxycycline were not active (62.5–100.0% resistance) *in vitro* against gram-negative *Enterobacteriaceae* isolates carrying *tet* genes

Conclusions

- Omadacycline demonstrated MIC_{50} values of 0.06–0.12 µg/mL and 1–4 µg/mL against the population of gram-positive and -negative clinical isolates or subsets having *tet* genes, respectively
- These results indicate that omadacycline potency is not adversely affected against molecularly characterized gram-positive clinical isolates carrying commonly acquired *tet* genes
  - The MIC distributions against molecularly characterized gram-negative clinical isolates were shifted higher than those observed against the wild-type control set for both omadacycline and tigecycline (Figure 2). This may be due to the presence of additional resistance mechanisms (e.g. permeability) other than *tet* genes

Figure 1 MIC distribution for omadacycline (OMC), tetracycline (TET), doxycycline (DOX), and tigecycline (TIG) against (A) wild-type gram-positive organisms and (B) those carrying *tet*(K), (C) *tet*(L) and *tet*(M) and (D) *tet*(M)

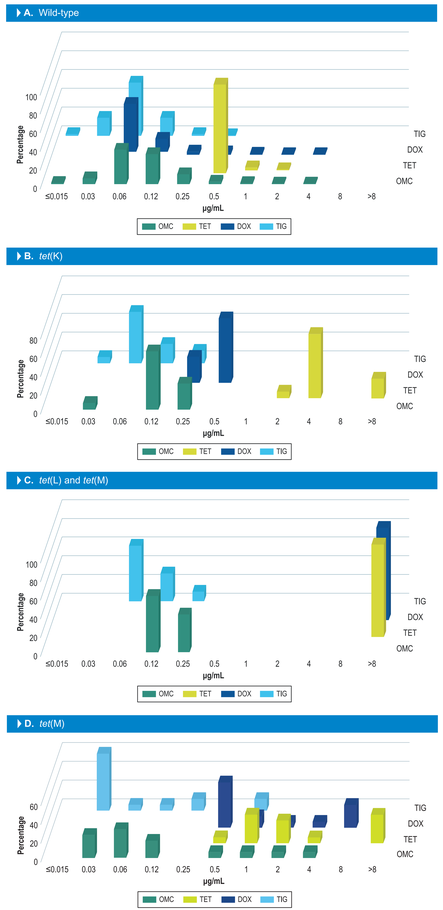

Figure 2 MIC distribution for omadacycline (OMC), tetracycline (TET), doxycycline (DOX), and tigecycline (TIG) against (A) wild-type gram-negative organisms and (B) those carrying *tet*(A), (C) *tet*(A) and *tet*(D), (D) tet(B), (E) *tet*(D) and (F) other *tet* genes

Acknowledgements

This study was sponsored by Paratek Pharmaceuticals, Inc., King of Prussia, PA.

References

Clinical and Laboratory Standards Institute (2017). *M100Ed27E. Performance standards for antimicrobial susceptibility testing: 27th Informational Supplement.* Wayne, PA, USA.

Clinical and Laboratory Standards Institute (2015). *M07-A10.* Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically; Approved Standard—10th Edition. Wayne, USA.

EUCAST (2017). Breakpoint tables for interpretation of MICs and zone diameters. Version 7.0, January 2017. Available at http://www.eucast.org/clinical_breakpoints/. Accessed January 2017.

Tygacil® Package Insert, Wyeth Pharmaceuticals (2015). Available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/021821s045lbl.pdf

Pfaller MA, Huband MD, Shortridge D, Flamm RK (2018). Surveillance of Omadacycline Activity Tested against Clinical Isolates from the United States and Europe as Part of the 2016 SENTRY Antimicrobial Surveillance Program. *Antimicrob Agents Chemother.* 62: e02327-17.