AAR-520, 6/17/23

In Vitro Activity of Omadacycline Against Clinical Isolates of *Nocardia*

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Abstract (Revised)

Background:
First-line regimens for nocardiosis are associated with considerable toxicity and alternative therapies are needed. Omadacycline is an aminomethylcycline with broad antimicrobial activity that can be administered orally or intravenously, whose *in vitro* activity against *Nocardia* species has not been formally assessed.

Methods:
Nocardia species identification was performed at ARUP Laboratories by MALDI-TOF (Bruker Biotyper) or 16S rRNA gene sequencing or was determined prior to submission by client laboratories. Antimicrobial susceptibility testing (AST) was performed on *Nocardia* species isolates, using 96-well frozen reference broth microdilution (BMD) panels, and minimal inhibitory concentrations (MICs) determined according to CLSI M24S guidelines. Isolates from a range of clinical specimens including respiratory, cutaneous, body fluid, and central nervous system sources were included. Quality control was performed using *Nocardia nova* ATCC BAA-2227 and *Staphylococcus aureus* ATCC 29213. Results were included only if the QC values were within range. The MIC_{50}, MIC_{90}, and MIC ranges of omadacycline and comparator antimicrobials for each *Nocardia* species were determined.

Results:
AST was completed for 301 isolates, including 24 different *Nocardia* species. The most common *Nocardia* species tested were *N. cyriacigeorgica*, *N. nova*, and *N. farcinica*. Omadacycline MICs across all *Nocardia* species ranged from 0.06 to 8 mg/L. Omadacycline was most active against *N. paucivorans* (MIC_{50} = 0.25 mg/L, MIC_{90} = 0.25 mg/L), and *N. asiatica* (MIC_{50} = 0.25 mg/L, MIC_{90} = 1 mg/L). Omadacycline was least active against *N. farcinica* (MIC_{50} = 4 mg/L, MIC_{90} = 8 mg/L).

Conclusions:
Omadacycline exhibits species-specific activity against clinical *Nocardia* species isolates. The lowest omadacycline MICs were observed for *N. paucivorans, N. asiatica, N. abscessus* complex, and *N. beijingensis*. Further studies of the potential clinical utility of omadacycline for treatment of nocardiosis are warranted.

Discussion

- Oral options are desirable for nocardiosis, however long-term options are often limited
  - *Nocardia* spp. demonstrated nearly 100% susceptibility to TMP-SMX and linezolid, but long-term use is limited by significant adverse effects
  - *Nocardia* spp. may be resistant to other options such as fluoroquinolones, minocycline, and amoxicillin-clavulanate
- Omadacycline may be a desirable alternative given its oral formulation, once-daily dosing, low potential for drug-drug interactions, and favorable tolerability profile
- Omadacycline exhibited similar *in vitro* activity compared to minocycline and tigecycline
- To date, omadacycline CNS penetration data are limited and do not support use for CNS disease
- No significant trailing was observed for omadacycline
- BMD reproducibility was demonstrated for omadacycline, with 10 isolates tested in triplicate revealing MIC values within 1 two-fold dilution

Results

***Nocardia* Species Distribution**

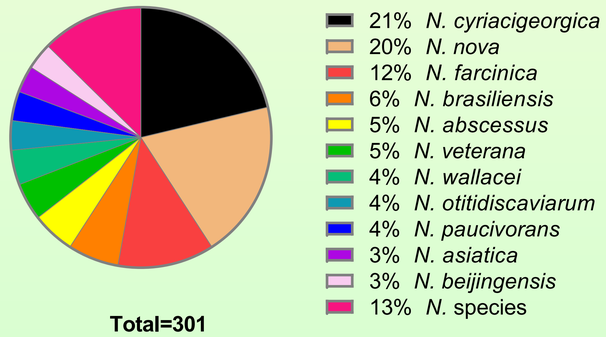

Figure 1: *Nocardia* are listed to the species-level if there were ≥ 10 isolates tested. All other *Nocardia* spp. are listed as "*Nocardia* species," the most common of which were *N. vulneris* (n=6), *N. asteroides* (n=4), and *N. transvalensis* complex (n=4).

Table 1: Total *Nocardia* species Susceptibility Patterns

Total *Nocardia* species (n=301)	CIP	IMI	TMP/SMX	AMI	CRO	LZD	MIN
Susceptible (%)	17	64	99	97	63	100	35
Intermediate (%)	7	10	-	-	19	-	64
Resistant (%)	76	26	1	3	18	0	1

-: No intermediate breakpoint interpretations per CLSI M24S guidelines for *Nocardia* spp.
CIP = Ciprofloxacin; IMI = Imipenem; TMP/SMX = Trimethoprim-Sulfamethoxazole; AMI = Amikacin; CRO = Ceftriaxone; LZD = Linezolid; MIN = Minocycline

Table 2: *Nocardia* MIC Patterns for Minocycline, Omadacycline, and Tigecycline by Species

		Minocycline			Omadacycline		Tigecycline	
Organism	Isolates Tested	Susceptible (%)* MIC ≤ 1	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Nocardia abscessus complex	16	100	0.5	1	0.5	1	0.25	0.5
Nocardia asiatica	10	100	0.25	0.5	0.25	1	0.25	1
Nocardia beijingensis	10	100	0.25	1	0.5	2	1	2
Nocardia brasiliensis	19	53	1	4	2	2	0.25	0.5
Nocardia cyriacigeorgica	64	14	2	4	2	4	1	2
Nocardia farcinica	36	0	2	4	4	8	4	4
Nocardia nova	59	20	2	4	4	4	1	2
Nocardia otitidiscaviarum	11	55	1	2	1	2	0.5	1
Nocardia paucivorans	11	100	0.25	0.25	0.25	0.25	0.25	0.5
Nocardia veterana	14	14	2	4	4	4	2	4
Nocardia wallacei	13	31	2	2	4	4	2	4
Nocardia spp.	38	40	2	4	2	4	0.5	4
Total *Nocardia* isolates	301	35	2	4	2	4	1	4

*: Minocycline is the only antibiotic in the tetracycline class with breakpoint interpretations per CLSI M24S guidelines for *Nocardia* spp.
The shaded colors indicate the spectrum of MIC values and not interpretation categories. Blue correlates to lower MICs, whereas red correlates to higher MICs.
The BMD panels evaluated a range from 0.015-32 mg/L for minocycline, omadacycline, and tigecycline.

Conclusions

- *In vitro* potency differed by species among *Nocardia* clinical isolates
- Omadacycline was most active against *N. paucivorans, N. abscessus* complex, *N. asiatica,* and *N. beijingensis*
- Further studies of the potential clinical utility of omadacycline for the treatment of nocardiosis are warranted

References / Acknowledgments

We would like to thank Paratek Pharmaceuticals for funding this investigator-initiated grant and our co-workers at ARUP Laboratories for performing isolate identification and MIC determinations.

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