AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Antimicrobial Chemotherapy | Full-Length Text

In vitro activity of omadacycline against clinical isolates of *Nocardia*

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ABSTRACT Nocardiosis typically requires a prolonged treatment duration of ≥6 months and initial combination therapy with 2–3 antibiotics. First-line regimens for nocardiosis are associated with considerable toxicity; therefore, alternative therapies are needed. Omadacycline is an aminomethylcycline with broad antimicrobial activity whose *in vitro* activity against *Nocardia* species has not been formally assessed. The *in vitro* potency of omadacycline was evaluated against 300 *Nocardia* clinical isolates by broth microdilution. The most common *Nocardia* species tested were *N. cyriacigeorgica* (21%), *N. nova* (20%), and *N. farcinica* (12%). The most common specimens were respiratory (178 isolates, 59%) and wound (57 isolates, 19%). Omadacycline minimum inhibitory concentrations (MICs) across all *Nocardia* species ranged from 0.06 µg/mL to 8 µg/mL, with an MIC_{50} of 2 µg/mL and MIC_{90} of 4 µg/mL. The lowest MICs were found among *N. paucivorans* (MIC_{50} = 0.25 µg/mL, MIC_{90} = 0.25 µg/mL), *N. asiatica* (MIC_{50} = 0.25 µg/mL, MIC_{90} = 1 µg/mL), *N. abscessus* complex (MIC_{50} = 0.5 µg/mL, MIC_{90} = 1 µg/mL), *N. beijingensis* (MIC_{50} = 0.5 µg/mL, MIC_{90} = 2 µg/mL), and *N. otitidiscaviarum* (MIC_{50} = 1 µg/mL, MIC_{90} = 2 µg/mL). The highest MICs were found among *N. farcinica* (MIC_{50} = 4 µg/mL, MIC_{90} = 8 µg/mL). *In vitro* potency differed by species among *Nocardia* clinical isolates. Further studies are warranted to evaluate the potential clinical utility of omadacycline for nocardiosis.

KEYWORDS *Nocardia*, omadacycline, antimicrobial susceptibility

Nocardia species are a diverse group of ubiquitous, aerobic, partially acid-fast, filamentous, Gram-positive bacilli (1–3). There are more than 100 recognized *Nocardia* species; approximately half are known human pathogens (4–6). Infections occur predominantly in patients with impaired cell-mediated immunity, typically via inhalation from the environment, and most frequently manifest as respiratory tract infections (7–10). Extrapulmonary disease is common, occurring in ~30%–40% of patients, with the central nervous system (CNS) and skin and subcutaneous tissue being the most common dissemination sites, with each occurring in ~10%–30% of patients (7–11).

Trimethoprim-sulfamethoxazole (TMP-SMX) at higher, weight-based doses for 6–12 months or longer has long been the standard of care for nocardiosis (1, 2, 5, 12). Guidelines recommend the addition of a second and occasionally a third agent for severe or disseminated nocardiosis. The selection of these regimens is highly individualized based on several factors such as the *Nocardia* species involved, site of infection (e.g., need for CNS penetration), side effects, and drug interaction profile of the antimicrobials (2). Oral antimicrobials are desired given their ease of administration and to prevent complications from long-term central venous catheter access. Antimicrobials frequently considered for use in combination with TMP-SMX include linezolid, ceftriaxone, imipenem-cilastatin, meropenem, amikacin, minocycline, and fluoroquinolones. Because of long treatment durations and aggressive dosing schemes, often in

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R.J.B. reports receiving prior research support from Rempex Pharmaceuticals. The other authors have no relevant conflicts of interest to disclose.

See the funding table on p. 7.

Received 19 December 2023
Accepted 8 March 2024
Published 27 March 2024

combination regimens, drug toxicity occurs in 17%–67% of patients (9, 13–15). Indeed, a high proportion of patients require therapy modification because of drug toxicity. Additionally, many of these first-line therapies can only be administered parenterally, which complicates outpatient management.

The tetracyclines minocycline, doxycycline, and glycylcycline tigecycline all have *in vitro* activity against several species of *Nocardia*. Omadacycline, a first-in-class aminomethylcycline derived from minocycline, displays activity against a broad range of bacteria (16, 17). It possesses *in vitro* and *in vivo* activity against rapidly growing mycobacteria (RGM), such as *Mycobacteroides abscessus* (18–22). Due to their phylogenetic relatedness, it is reasonable to suspect that omadacycline could also have activity against *Nocardia* species. Omadacycline may be a desirable option for treating nocardiosis given its oral formulation, once-daily dosing, low potential for drug-drug interactions, and favorable tolerability profile. Given the potential clinical advantages of omadacycline and the need for additional therapies for nocardiosis, this study aimed to determine the *in vitro* activity of omadacycline and comparator antimicrobials against a diverse collection of clinical *Nocardia* isolates.

MATERIALS AND METHODS

Clinical isolates

Clinical isolates were referred to Associated Regional and University Pathologists (ARUP) Laboratories from institutions throughout the United States for identification and/or routine susceptibility testing. Isolates that were identified as *Nocardia* spp. between February 2018 and April 2023 were eligible for inclusion in this study. Isolates were identified by matrix-assisted laser desorption ionization-time of flight mass spectrometry (Bruker Biotyper, Billerica, MA, USA), 16s rRNA gene sequencing, or by client laboratories (23, 24). Isolates from a range of clinical specimens including respiratory, wound, body fluid, blood, CNS, and ocular sources were included. *Nocardia* spp. isolates were selected for inclusion in this study based on the frequency of isolation, availability through routine laboratory testing or laboratory isolate archives, and to achieve a broad diversity of species.

Antimicrobial susceptibility testing

Antimicrobial susceptibility testing (AST) was performed on 300 *Nocardia* isolates. For the less common *Nocardia* species, archived isolates were used after sub-culturing twice onto sheep blood agar plates. AST was performed using 96-well frozen reference broth microdilution (BMD) panels in cation-adjusted Mueller-Hinton broth (CAMHB) (Thermo Fisher) according to CLSI M24, third ed. (25). Briefly, isolate suspensions were normalized to 0.5 McFarland in sterile water, diluted in CAMHB to achieve a final inoculum of 1–5 × 10^4 CFU/well, covered with adhesive seals and incubated for up to 5 days. Minimum inhibitory concentrations (MICs) were determined at 48 hours for imipenem and when at least 2+ growth was observed in control wells (25), according to CLSI M24S-2 guidelines (26). The antimicrobials, and range of concentrations tested, included omadacycline (0.015–32 µg/mL), tigecycline (0.015–32 µg/mL), minocycline (0.015–32 µg/mL), TMP-SMX (0.03/0.59–16/304 µg/mL), linezolid (0.12–32 µg/mL), ceftriaxone (0.25–128 µg/mL), imipenem (0.12–64 µg/mL), amikacin (0.06–32 µg/mL), and ciprofloxacin (0.06–32 µg/mL). MICs with interpretations were determined for minocycline, TMP-SMX, linezolid, ceftriaxone, imipenem, amikacin, and ciprofloxacin (26). MICs alone were determined for omadacycline and tigecycline, given the absence of breakpoints in the CLSI M24S-2 guidelines. Ten isolates representing eight different *Nocardia* species *[N. wallacei*, *N. veterana*, *N. transvalensis*, *N. farcinica*, *N. cyriacigeorgica* (two isolates), *N. beijingensis* (two isolates), *N. nova*, *N. abscessus* complex] were tested in triplicate to evaluate reproducibility. No significant trailing was encountered when interpreting omadacycline MICs from BMD, even with slower-growing species; therefore, MICs were read at 100% inhibition (18, 26).

Quality control

In accordance with the CLSI M24S-2 guidelines, quality control (QC) was performed using *Nocardia nova* ATCC BAA-2227 and *Staphylococcus aureus* ATCC 21213 (26). Results were included only if the QC values were within range. Omadacycline and tigecycline MICs were determined for *Nocardia nova* ATCC BAA-2227 for a total of 18 independent replicates; however, the CLSI M24S-2 does not include omadacycline or tigecycline QC ranges for this reference strain.

Data analysis

The MIC ranges, MIC_{50}, and MIC_{90} of omadacycline, tigecycline, and minocycline were determined for each species of *Nocardia*, and the percentage of susceptibility was determined for comparator antimicrobials. Figures were created using the ggplot2 package in R version 4.2.2 (27).

RESULTS

AST was performed for 300 *Nocardia* clinical isolates, covering 28 different species. The majority of isolates (216, 72%) were identified by ARUP Laboratories with the remainder identified by client laboratories. The most common *Nocardia* species tested were *N. cyriacigeorgica* (64 isolates, 21%), *N. nova* (59 isolates, 20%), and *N. farcinica* (36 isolates, 12%). Specimen sources included respiratory (178 isolates, 59%), wound (57 isolates, 19%), body fluid (17 isolates, 6%), blood (10 isolates, 3%), CNS (5 isolates, 2%), and ocular (4 isolates, 1%), while 29 isolates (10%) were from undisclosed sources.

Omadacycline MICs across all *Nocardia* species ranged from 0.06 µg/mL to 8 µg/mL (Table 1). When evaluating all *Nocardia* isolates, omadacycline displayed an MIC_{50} of 2 µg/mL and MIC_{90} of 4 µg/mL. Omadacycline was most active against *N. paucivorans* (MIC_{50} = 0.25 µg/mL, MIC_{90} = 0.25 µg/mL), *N. asiatica* (MIC_{50} = 0.25 µg/mL, MIC_{90} = 1 µg/mL), *N. abscessus* complex (MIC_{50} = 0.5 µg/mL, MIC_{90} = 1 µg/mL), *N. beijingensis* (MIC_{50} = 0.5 µg/mL, MIC_{90} = 1 µg/mL), and *N. otitidiscaviarum* (MIC_{50} = 1 µg/mL, MIC_{90} = 2 µg/mL). Omadacycline was least active against *N. farcinica* (MIC_{50} = 4 µg/mL, MIC_{90} = 8 µg/mL).

Among comparator drugs, TMP-SMX, linezolid, and amikacin displayed the best *in vitro* activity with 98.7%, 99.7%, and 96.7% of isolates testing susceptible, respectively (Table 2). Minocycline is the only tetracycline in this study with breakpoint interpretations in the CLSI M24S-2 (26), and minocycline susceptibility varied widely (0%–100%) depending on the *Nocardia* species. In general, omadacycline, tigecycline, and minocycline displayed similar activities against each *Nocardia* species, tracking within one twofold dilution of each other. The MIC_{50} and MIC_{90} of omadacycline against all *Nocardia* species were 2 µg/mL and 4 µg/mL, respectively; tigecycline: 1 µg/mL and 4 µg/mL, respectively; and minocycline: 2 µg/mL and 4 µg/mL, respectively. Regarding the five species for which omadacycline was found to have the most potent *in vitro* activity (*N. paucivorans*, *N. asiatica*, *N. abscessus* complex, *N. beijingensis*, *and N. otitidiscaviarum*), minocycline was found to have 100%, 100%, 100%, 100%, and 54.5% susceptibility, respectively.

Notably, the CLSI M24S-2 guidelines do not include omadacycline or tigecycline QC ranges for the reference strain *Nocardia nova* ATCC BAA-2227 (26). To assess this strain's suitability for QC of these agents, MICs for omadacycline and tigecycline were determined across 18 independent replicates. MICs for omadacycline ranged from 2 µg/mL to 4 µg/mL and MICs for tigecycline ranged from 1 µg/mL to 2 µg/mL (Fig. 1). Omadacycline BMD testing was shown to be reproducible with all MIC values within one twofold dilution across triplicate results from 10 clinical isolates representing eight species.

TABLE 1 Omadacycline MICs observed against *Nocardia* species

Species	Number of isolates tested	Omadacycline MIC (µg/mL)												MIC_{50}	MIC_{90}	MIC range
		0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16	32			
N. abscessus complex	16			1		2	7	5	1					0.5	1	0.06–2
N. asiatica	10			1	2	2	3	2						0.25	1	0.06–1
N. beijingensis	10				2	2	1	3	1	1				0.5	2	0.12–4
N. brasiliensis	19					1	3	4	11					2	2	0.25–2
N. cyriacigeorgica	64						2	9	30	23				2	4	0.5–4
N. farcinica	36								1	27	8			4	8	2–8
N. nova	59						1	6	18	29	5			4	4	0.5–8
N. otitidiscaviarum	11					1	3	3	4					1	2	0.25–2
N. paucivorans	11				3	8								0.25	0.25	0.12–0.25
N. veterana	14								4	10				4	4	2–4
N. wallacei	12					1	1		1	8	1			4	4	0.25–8
Nocardia species[a]	38			1	1	3	4	2	15	11	1			2	4	0.06–8
Total *Nocardia* isolates	300			3	8	20	25	34	86	109	15			2	4	0.06–8

[a]*Nocardia* species includes species with ≤6 isolates and *Nocardia* spp. that could not be identified to species level. This group consisted of *N. vulneris* (*n* = 6), *N. asteroides* (*n* = 4), *N. transvalensis* complex (*n* = 4), *N. africana/nova* (*n* = 3), *N. pseudobrasiliensis* (*n* = 3), *N. brasiliensis/vulneris* (*n* = 2), *N. farcinica/kroppenstedtii* (*n* = 2), *N. africana* (*n* = 1), *N. amikacinitolerans* (*n* = 1), *N. araoensis* (*n* = 1), *N. araoensis/niwae* (*n* = 1), *N. carnea* (*n* = 1), *N. grenadensis* (*n* = 1), *N. rhamnosiphila* (*n* = 1), *N. sienata* (*n* = 1), *N. thailandica* (*n* = 2), *N. vinacea* (*n* = 1), and *Nocardia* spp. (*n* = 3).

TABLE 2 Antimicrobial susceptibility of omadacycline and comparators against various *Nocardia* species[c]

Species	No. tested	OMC[a]		TGC[a]		MIN			SXT	LZD	AXO	IMI	AMI	CIP
		MIC_{50}[b]	MIC_{90}	MIC_{50}	MIC_{90}	MIC_{50}	MIC_{90}	% S	% S	% S	% S	% S	% S	% S
N. abscessus complex	16	0.5	1	0.25	0.5	0.5	1	100	100	100	100	25	100	0
N. asiatica	10	0.25	1	0.25	1	0.25	0.5	100	100	100	90	70	100	0
N. beijingensis	10	0.5	2	1	2	0.25	1	100	100	100	100	90	100	0
N. brasiliensis	19	2	2	0.25	0.5	1	4	52.6	100	100	52.6	5.3	100	5.3
N. cyriacigeorgica	64	2	4	1	2	2	4	14.1	100	100	84.4	82.8	98.4	0
N. farcinica	36	4	8	4	4	2	4	0	97.2	100	2.8	44.4	100	47.2
N. nova	59	4	4	1	2	2	4	20.3	100	100	66.1	98.3	100	0
N. otitidiscaviarum	11	1	2	0.5	1	1	2	54.5	100	100	0	0	100	0
N. paucivorans	11	0.25	0.25	0.25	0.5	0.25	0.25	100	100	100	100	100	100	100
N. veterana	14	4	4	2	4	2	4	14.3	100	100	35.7	100	100	0
N. wallacei	12	4	4	2	4	2	2	33.3	75	100	75	8.3	41.7	100
Nocardia species[d]	38	2	4	0.5	4	2	4	39.5	100	100	65.8	52.6	94.7	26.3
Total *Nocardia* isolates	300	2	4	1	4	2	4	35	98.7	99.7	63	64.7	96.7	17

[a]There are no breakpoint interpretations for omadacycline and tigecycline against *Nocardia* species in the CLSI M24S-2; therefore, only the MIC_{50} and MIC_{90} are reported.
[b]MIC values are reported in units of µg/mL.
[c]OMC: omadacycline, MIN: minocycline, TGC: tigecycline, SXT: trimethoprim-sulfamethoxazole, LZD: linezolid, CIP: ciprofloxacin, IMI: imipenem, AXO: ceftriaxone, CIP: ciprofloxacin, AMI: amikacin.
[d]*Nocardia* species includes species with ≤6 isolates and *Nocardia* spp. that could not be identified to species level. This group consisted of *N. vulneris* (*n* = 6), *N. asteroides* (*n* = 4), *N. transvalensis* complex (*n* = 4), *N. africana/nova* (*n* = 3), *N. pseudobrasiliensis* (*n* = 3), *N. brasiliensis/vulneris* (*n* = 2), *N. farcinica/kroppenstedtii* (*n* = 2), *N. africana* (*n* = 1), *N. amikacinoitolerans* (*n* = 1), *N. araoensis* (*n* = 1), *N. araoensis/niwae* (*n* = 1), *N. carnaea* (*n* = 1), *N. grenadensis* (*n* = 1), *N. rhamnosiphila* (*n* = 1), *N. sienata* (*n* = 1), *N. thailandica* (*n* = 2), *N. vinacea* (*n* = 1), and *Nocardia* spp. (*n* = 3).

DISCUSSION

In this susceptibility study evaluating the *in vitro* activity of omadacycline against a large set of clinical *Nocardia* isolates, omadacycline activity was shown to vary between species. Omadacycline was most active against *N. paucivorans*, *N. asiatica*, *N. abscessus* complex, *N. beijingensis*, and *N. otitidiscaviarum*, whereas it was least active against *N. farcinica*. MIC distributions were generally within one twofold dilution of minocycline and tigecycline.

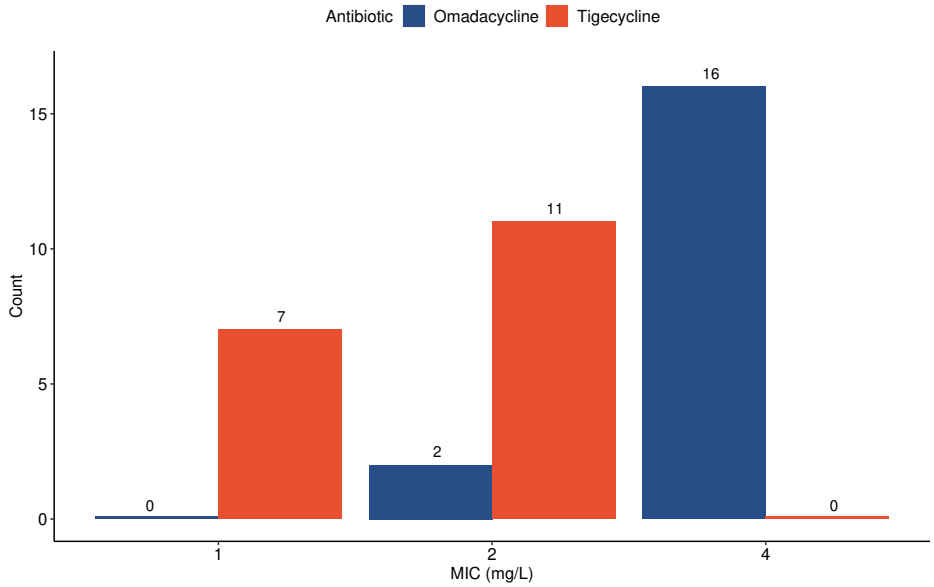

FIG 1 Distribution of omadacycline and tigecycline MICs against reference QC strain *N. nova* ATCC BAA-2227. Because QC ranges have not been established for tigecycline or omadacycline, we performed 18 independent replicate reference BMD tests using the CLSI *Nocardia nova* QC organism. All MICs were 1–2 µg/mL for tigecycline and 2–4 µg/mL for omadacycline.

There is a paucity of high-quality randomized controlled trials to support evidence-based recommendations for *Nocardia* infections (2). Thus, selection of initial antibiotic regimens is individualized based on clinical presentation (site and severity of infection), immunocompromised state, *Nocardia* species involved, drug-drug interactions, and pharmacokinetic-pharmacodynamic advantages of a selected regimen. A combination of two or three active agents is typically recommended for severe, disseminated, or life-threatening forms of nocardiosis, consisting of high-dose TMP-SMX, an oxazolidinone, and an intravenous agent such as meropenem, imipenem, or ceftriaxone. Based on disease burden, severity at presentation, and clinical response, a lengthy duration of therapy (6–12 months or longer) is usually recommended for nocardiosis in immunocompromised hosts (2). The necessity for prolonged antimicrobial therapy with multiple agents often leads to treatment-associated adverse effects and organ toxicities. Additionally, populations at risk for nocardiosis often have concomitant therapies such as immunosuppressive agents, antimicrobial prophylactic agents, and chemotherapy that place them at risk for additive toxicities, including acute kidney injury and myelosuppression. Consequently, treatment discontinuation rates for TMP-SMX-based regimens have been reported to be greater than 50% (14, 28) due to poor gastrointestinal tolerance, renal toxicity, electrolyte imbalances, and myelosuppression. Similarly, the risk for adverse events with linezolid—particularly myelosuppression and mitochondrial toxicity (including lactic acidosis and peripheral and optic neuropathy)—increases with length of therapy, frequently leading to premature discontinuation of linezolid during the treatment of *Nocardia* infections (29, 30). Due to the safety profile of omadacycline and other tetracyclines, their regulatory approval in pneumonia and skin-soft tissue infections, and the immunomodulatory effects of this class of antibiotics, omadacycline may constitute a feasible option for consolidation of long-term therapy either as a single agent or in combination once susceptibility testing is available. Moreover, our study results support omadacycline empirical therapy for cases involving *N. paucivorans*, *N. asiatica*, *N. beijingensis*, *N. abscessus* complex, or *N. otitidiscaviarum*. Lastly, for those patients whose risk for renal and hematological toxicities limits the initial use of TMP-SMX or linezolid, our study supports consideration of omadacycline as a therapeutic option in combination with other active agents, for cases where *N. paucivorans*, *N. asiatica*, *N. beijingensis*, *N. abscessus* complex, or *N. otitidiscaviarum* are suspected or confirmed.

Minocycline is the only tetracycline antibiotic in this study with clinical breakpoints against *Nocardia* species available in the CLSI M24S-2 (26). Thus far, there are no breakpoints for omadacycline against *Nocardia* species because, heretofore, there has been a dearth of MIC data to establish epidemiologic cutoff values as well as a lack of published clinical experience treating nocardiosis with omadacycline. Like other tetracyclines, omadacycline has demonstrated an area-under-the-curve (AUC)-dependent killing effect (31–33). Based on hollow fiber model studies, the exposures associated with the standard oral dose of omadacycline of 300 mg daily have been suggested to be effective for pulmonary infections due to non-tuberculous mycobacteria with omadacycline MICs between 1 µg/mL and 4 µg/mL (31, 32, 34). While no head-to-head pharmacokinetic studies are available comparing omadacycline to minocycline, free plasma AUCs are approximately similar between the two agents at their respective standard dosing schemes (35–37), although variable, concentration-dependent protein binding with minocycline makes comparison of free drug exposures between agents challenging (38). Even though omadacycline and tigecycline were shown to have comparable MIC patterns across the different *Nocardia* species, pharmacokinetic differences between the two drugs may favor omadacycline when MICs are identical. Omadacycline was found to have approximately threefold higher concentrations than tigecycline in plasma, epithelial lining fluid, and alveolar cells

Trailing endpoints are a well-known phenomenon when reading MICs for TMP-SMX and linezolid, making the determination of MICs problematic (25). Brown-Elliott and Wallace performed *in vitro* susceptibility testing of omadacycline against both RGM and

slowly growing mycobacteria (SGM) and found considerable trailing for omadacycline against RGM, but not for SGM (18). In our study, no significant trailing was identified when reading MICs. All QC isolates tested with omadacycline and comparator agents were within the CLSI M24S-2 acceptable ranges. Although there is no QC reference range for omadacycline against *N. nova* ATCC BAA-2227, the MICs for omadacycline against 18 replicates were all within one twofold dilution (2–4 µg/mL). Additionally, when 10 isolates across eight species were tested in triplicate, the MIC values were all within one twofold dilution. Altogether, the above results demonstrate the reproducibility of omadacycline MIC determinations with frozen reference BMD.

One limitation of our study is the potential degradation of omadacycline throughout the process of susceptibility testing. For instance, Shankar et al. discovered that intact omadacycline concentrations declined by approximately 50% in 24 hours, and this degradation can lead to falsely elevated MICs against SGM species that require prolonged AST incubation times (39). However, the impact on observed MICs in *M. abscessus*, an RGM similar to *Nocardia* in its doubling times, was minimal. Most of our MIC interpretations were read at 72 hours per CLSI M24S-2 guidelines, and it was rarely necessary to incubate longer. Thus, we expect that drug degradation did not significantly affect the omadacycline MIC results in this study.

Based on our results and its favorable pharmacologic properties, omadacycline may be a desirable therapeutic option for nocardiosis caused by certain *Nocardia* species. Further studies, including clinical trials, are needed to evaluate the potential clinical utility and role of omadacycline for the treatment of nocardiosis.

ACKNOWLEDGMENTS

We would like to thank our co-workers at ARUP Laboratories for performing isolate identification and assisting with susceptibility testing.

This research was supported by an investigator-initiated research grant from Paratek Pharmaceuticals, Inc. The sponsor reviewed the study design and final manuscript draft, but final decisions on the design and content of the manuscript were the responsibility of the authors.

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FUNDING

Funder	Grant(s)	Author(s)
Paratek Pharmaceuticals		Mark Fisher
		Russell J. Benefield
		Carlos A. Gomez

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Jonathan Pham, Data curation, Formal analysis, Investigation, Validation, Writing – original draft, Writing – review and editing | Russell J. Benefield, Conceptualization, Funding acquisition, Methodology, Project administration, Supervision, Visualization, Writing – original draft, Writing – review and editing | Natali Baker, Investigation, Writing – original draft, Writing – review and editing | Shane Lindblom, Investigation, Writing – original draft, Writing – review and editing | Nicholas Canfield, Investigation, Writing – original draft, Writing – review and editing | Carlos A. Gomez, Conceptualization, Funding acquisition, Methodology, Writing – original draft, Writing – review and editing | Mark Fisher, Conceptualization, Data curation, Formal analysis, Funding acquisition, Methodology, Project administration, Resources, Supervision, Writing – original draft, Writing – review and editing

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