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Taylor Morrisette
Wayne State University

Sara Alosaimy
Wayne State University

Julie V. Philley
University of Texas Health Science Center at Tyler, jphilley@uttyler.edu

Carly Wadle
University of Texas Health Science Center at Tyler

Catessa Howard

See next page for additional authors

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Author

Taylor Morrisette, Sara Alosaimy, Julie V. Philley, Carly Wadle, Catessa Howard, Andrew J. Webb, Michael P. Veve, Melissa L. Barger, Jeannette Bouchard, Tristan W. Gore, Abdalhamid M. Lagnf., Iman Ansari, Carlos Mejia-Chew, Keira A. Cohen, and Michael J. Rybak

Preliminary, Real-world, Multicenter Experience With Omadacycline for *Mycobacterium abscessus* Infections

Taylor Morrisette,¹ Sara Alosaimy,¹ Julie V. Philley,² Carly Wadle,² Catessa Howard,³ Andrew J. Webb,^{4,5} Michael P. Veve,^{6,7} Melissa L. Barger,⁸ Jeannette Bouchard,⁹ Tristan W. Gore,⁹ Abdalhamid M. Lagnf,¹ Iman Ansari,¹ Carlos Mejia-Chew,¹⁰ Keira A. Cohen,¹¹ and Michael J. Rybak^{1,12,13}

¹Anti-Infective Research Laboratory, Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA, ²Division of Pulmonary and Critical Care Medicine, University of Texas Health Science Center, University of Texas, Tyler, Texas, USA, ³Department of Pharmacy, West Virginia University Medicine, Morgantown, West Virginia, USA, ⁴Department of Pharmacy, Mayo Clinic, Rochester, Minnesota, USA, ⁵Department of Pharmacy, Oregon Health & Science University, Portland, Oregon, USA, ⁶Department of Clinical Pharmacy and Translational Science, College of Pharmacy, University of Tennessee Health Science Center, Knoxville, Tennessee, USA, ⁷Department of Pharmacy, University of Tennessee Medical Center, Knoxville, Tennessee, USA, ⁸Department of Medicine, Ventura County Medical Center, Ventura, California, USA, ⁹College of Pharmacy, University of South Carolina, Columbia, South Carolina, USA, ¹⁰Division of Infectious Diseases, Department of Medicine, Washington University School of Medicine, St. Louis, Missouri, USA, ¹¹Division of Pulmonary and Critical Care Medicine, Johns Hopkins University School of Medicine, Baltimore, Maryland, USA, ¹²Department of Medicine, Division of Infectious Diseases, School of Medicine, Wayne State University, Detroit, Michigan, USA and ¹³Department of Pharmacy Services, Detroit Receiving Hospital, Detroit Medical Center, Detroit, Michigan, USA

Twelve patients were treated with omadacycline (OMC) as part of a multidrug regimen for *Mycobacterium abscessus*. The majority of infections were of pulmonary origin (7/12; 58.3%). The median (interquartile range) duration of OMC was 6.2 (4.2–11.0) months. Clinical success occurred in 9/12 (75.0%) patients. Three patients experienced a possible adverse effect while on therapy.

Keywords. *Mycobacterium abscessus*; omadacycline; rapidly growing nontuberculous mycobacteria.

Nontuberculous mycobacteria (NTM) are opportunistic pathogens that are intrinsically resistant to many antimicrobials and lead to significant health care costs, morbidity, and mortality [1]. Specifically, *Mycobacterium abscessus* complex (composed of the subspecies *M. abscessus*, *M. bolletii*, and *M. massiliense*) is the most drug-resistant and pathogenic of the rapidly growing mycobacteria (RGM) and is very challenging to treat, partly owing to the varying resistance mechanisms between these subspecies (including to macrolides,

an important therapeutic for NTM treatment, if susceptible, and also available in an oral formulation) and prolonged treatment durations that are typically expensive [2]. Furthermore, a lack of clinical trials and minimally effective oral therapies lead to variations in how patients are treated and further compromise patient satisfaction, respectively [3]. It is crucial that novel antibiotics with optimal oral bioavailability, minimal adverse effects (AEs), and effectiveness against all subspecies of *M. abscessus* complex be discovered, developed, and clinically evaluated.

Omadacycline (OMC), a semisynthetic aminomethylcycline within the tetracycline (TCN) class, is available both in intravenous and oral formulations and is Food and Drug Administration (FDA) approved for community-acquired pneumonia and acute bacterial skin and skin structure infections [4]. Recent investigations have shown potent in vitro activity of OMC against drug-resistant *M. abscessus* complex clinical isolates, with observed minimum inhibitory concentration (MIC)₉₀ values similar to tigecycline (TGC) and eravacycline (ERV; intravenous-only glycylcycline and fluorocycline, respectively, within the TCN class) [5, 6]. However, limited studies have reported patient outcomes of those treated with OMC for *M. abscessus* infections [7]. The objective of this case series was to describe preliminary real-world experience of OMC for the treatment of *M. abscessus* infections.

METHODS

This was a multicenter, retrospective, observational case series at 6 geographically distinct medical centers in the United States in which OMC was initiated between January and August 2020. We included individuals aged ≥ 18 years with ≥ 1 *M. abscessus*-positive culture, in the setting of clinical suspicion for either pulmonary or extrapulmonary infection, who received OMC for ≥ 3 months with ≥ 3 months of documented NTM follow-up after OMC initiation. Patients were still included if negative circumstances (eg, OMC discontinued due to AE, death) precluded insufficient exposure or duration (< 3 months) of OMC continuation and/or follow-up.

Early clinical success was defined as a composite of survival, lack of clinical/radiographic worsening, lack of alteration of OMC therapy due to concerns for treatment failure, lack of microbiologic relapse (if patient has achieved culture conversion or microbiologic clearance and cultures were drawn), and lack of culture persistence for 3 consecutive positive cultures following OMC initiation (if patient has not had at least 2 negative cultures and cultures were drawn), which was evaluated throughout the required follow-up. We also reported intentions for OMC utilization and incidence of AE.

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Correspondence: Michael J. Rybak, PharmD, MPH, PhD, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, 259 Mack Avenue, Detroit, MI 48201 (m.rybak@wayne.edu).

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Microbiologic relapse was defined as 2 consecutive cultures positive for the same pathogen isolated from index culture following sputum culture conversion (respiratory) or microbiologic clearance (nonrespiratory). Sputum culture conversion was defined as having at least 3 consecutive negative sputum NTM cultures over 12 months. Microbiologic clearance was defined as having any negative culture following positive index culture (nonrespiratory). The Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints were applied, when applicable, for interpretation of MIC values, while the FDA antibacterial susceptibility interpretive criteria were used when information was not available via CLSI [8, 9]. Combination therapy was defined as any antibiotic used in tandem with OMC for ≥ 28 days. All adverse effects while on OMC were reported, although they could not be fully attributed to OMC due to combination regimens. Descriptive statistics were utilized for analysis using IBM SPSS software, version 26.0 (SPSS, Inc., Chicago, IL, USA).

RESULTS

Overall, 12 patients met inclusion criteria. Four individuals were excluded due to insufficient exposure to OMC (3/4) and/or insufficient duration of follow-up (4/4). Included individuals had a median age (interquartile range [IQR]) of 58 (54–63) years, they had a median body mass index (IQR) of 23.6 (21.1–28.9) kg/m², 50.0% were female, and 91.7% were Caucasian. Common comorbidities in those with nontuberculous mycobacterial pulmonary disease (NTM-PD) included interstitial lung disease (5/7; 71.4%), chronic obstructive pulmonary disease (2/7; 28.6%), asthma (2/7; 28.6%), and solid organ malignancy and/or acute myeloid leukemia (2/7; 28.6%), while no patients had cystic fibrosis or autoimmune disease. The majority of patients had insurance coverage through private entities (6/12; 50.0%), followed by Medicare (3/12; 25.0%; evaluated due to insurance coverage associated with selection of medications), and were treated with OMC strictly in the outpatient setting (10/12; 83.3%). Of patients included in this analysis, 5/12 (41.7%) had surgical interventions (debridement and/or incision and drainage).

The source of infection was primarily NTM-PD (7/12; 58.3%), followed by bone/joint (2/12; 16.7%). Three other extrapulmonary sites of infection involved an intra-abdominal infection, a skin and soft tissue infection, and an infected intravenous catheter. Of those with NTM-PD, the radiographic pattern was 57.1% (4/7) nodular bronchiectatic and 42.9% (3/7) fibrocavitary. Disseminated infection occurred in 2/12 (16.7%) of patients. The initial *M. abscessus* isolates were most commonly isolated from expectorated sputum (4/12; 33.3%), wound/tissue (4/12; 33.3%), or induced sputum (1/12; 8.3%). Of all included cases, 7/12 (58.3%) of isolates underwent subspeciation (6/7; 85.7% subspecies *M. abscessus*, 1/7; 14.3%

subspecies *M. massiliense*). *Erm* gene genotyping (genes that can express inducible macrolide resistance) was conducted in 9/12 (75.0%) isolates, with functional *erm* gene detected in 6/9 (66.7%) [2].

Before OMC initiation, antibiotic therapy was administered in 10/12 (83.3%) cases, for a median (IQR) of 4.7 (3.4–12.7) months (these data were calculated based on 11 patients, as data were not available for 1 patient). Mycobacterial cultures were positive at the time of OMC initiation in 6/9 (66.7%) patients for whom this information was known. Only a single isolate underwent MIC determination for OMC, which was 0.5 mcg/mL. However, TIG MICs were reported for 11/12 (91.7%) isolates (range, 0.06–1 mcg/mL; MIC₉₀, 1 mcg/mL). MIC values for other antibiotics are reported in [Supplementary Table 1](#).

The total median duration of OMC (IQR) was 6.2 (4.2–11.0) months, with the median duration of follow-up post-OMC initiation (IQR) being 5.1 (3.4–7.2) months. All patients received ≥ 2 companion antibiotics, with the most common being amikacin (8/12; 66.7%), imipenem (5/12; 41.7%), linezolid/tedizolid (5/12; 41.7%), azithromycin (4/12; 33.3%), and/or clofazimine (4/12; 33.3%). Interestingly, 2 patients received TIG concomitantly with OMC. Oral therapy was strictly utilized in all cases, with a loading dose of 450 mg once daily on days 1 and 2 used for initiation of therapy in 2/12 (16.7%) patients, while most patients did not receive a loading dose on initiation and received a maintenance dose of 300 mg once daily (10/12; 83.3%).

Clinical success occurred in 9/12 (75.0%) cases. Failures involved 3 cases with radiographic fibrocavitary and nodular bronchiectatic (plus dissemination) sources and skin and soft tissue sources. Other clinical and composite end point characteristics can be found in [Table 1](#). The primary reasons for OMC utilization were related to antimicrobial resistance to previous antibiotic(s) (8/12; 66.7%), previous antibiotic failure (6/12; 50.0%), ease of administration (6/12; 50.0%), and oral bioavailability of OMC (6/12; 50.0%).

Three patients experienced an AE while on therapy. One patient experienced a gastrointestinal AE (nausea/vomiting/diarrhea), and the OMC dose was reduced from 300 mg daily to 150 mg twice daily, with improvement in symptoms. Another patient experienced serum creatinine increase ≥ 0.5 mg/dL; OMC was temporarily discontinued, and this AE resolved. The third patient experienced AST/ALT elevations $>3\times$ the upper limit of normal; OMC was continued, despite these laboratory abnormalities, and the abnormalities resolved.

DISCUSSION

We report the largest real-world, observational, multicenter description of early treatment outcomes for patients treated with OMC for pulmonary and extrapulmonary *M. abscessus* infections with promising results. Due to the in vitro activity of OMC against *M. abscessus* and the available oral formulation,

Table 1. Clinical Characteristics of Patients Treated With Omadacycline for Various *Mycobacterium abscessus* Infections

Subject ID	Age/Sex/ Subspecies/ <i>Erm</i> Gene Presence	Infection Source (Dissemination)	TIG MIC, mg/L	Positive Culture When Switched to OMC?	Duration of Follow-up After OMC, mo	Duration of Follow-up After OMC Initiation, mo	Companion Drugs With OMC	Number of Negative Cultures After Initiation	Were Cultures Actually Drawn to Verify if They Were Negative?	Clinical Success	Death	Persistently Positive Culture	Microbiologic Relapse	Alteration of OMC Therapy due to Con- cerns of Failure	Clinical/Ra- diographic Worsening While on OMC
1	59/M/-/yes	IAI-multiple abscesses (no)	0.5	Unknown	11.7	11.3	Clofazimine, tedizolid	3	N/A	Yes	No	No	No	No	No
2	57/M/ massiliense/-	Hip bone/ joint + indwelling medical device (no)	1	Unknown	6.3	3.5	Azithromycin, clofazimine	1	N/A	Yes	No	No	No	No	No
3	68/F/-/	Fibrocartilaginous (no)	0.5	No	8.8	5.5	Azithromycin, tedizolid	0	No	Yes	No	-	-	No	No
4	49/F/abscessus/ yes	Fibrocartilaginous (no)	0.12	Yes	20.6	16.2	Amikacin, imipenem	1	N/A	Yes	No	No	No	No	No
5	80/M/ abscessus/no	Nodular bronchiectatic (no)	0.25	Yes	7.2	6.0	Amikacin, imipenem, linezolid	3	N/A	Yes	No	No	No	No	No
6	57/F/abscessus/ yes	Fibrocartilaginous (no)	0.25	Yes	5.4	3.3	Amikacin, clofazimine	0	Yes	No	No	Yes	N/A	No	No
7	63/F/abscessus/ no	Nodular bronchiectatic (no)	0.12	No	6.0	4.9	Amikacin, azithromycin, imipenem	2	N/A	Yes	No	No	No	No	No
8	53/M/ abscessus/ yes	Nodular bronchiectatic (yes-skin)	No	Yes	12.0	7.6	Amikacin, imipenem, tigecycline	4	N/A	Yes	No	No	No	No	No
9	26/M/ abscessus/ yes	Foot osteomyelitis (no)	1	Yes	3.3	3.3	Amikacin, meropenem, tigecycline	0	No	Yes	No	-	-	No	No
10	59/F/-/yes	SSTI (no)	0.25	Yes	5.4	5.2	Clofazimine, imipenem	3	N/A	No	No	No	No	No	Yes
11	55/F/-/	CLABSI (no)	0.06	No	3.8	3.7	Amikacin, tedizolid	1	N/A	Yes	No	No	No	No	No
12	62/M/-/no	Nodular bronchiectatic (yes-skin, liver)	0.06	Unknown	0.6	0.6 (died)	Amikacin, azithromycin, linezolid	0	No	No	Yes	-	-	No	Yes

Abbreviations: -, information not available; CLABSI, central line bloodstream infection; IAI, intra-abdominal infection; MIC, minimum inhibitory concentration; SSTI, skin and soft tissue infection; TIG, tigecycline.

it is expected that the medical community would have elevated curiosity about the use of OMC for patients with *M. abscessus*. Our results show similar (or slightly higher) preliminary results congruent with smaller reports of OMC and with other agent(s) used for *M. abscessus* infections, both in index and refractory disease [7, 10, 11]. Although the OMC treatment in its entirety was not included (as treatment is still ongoing for the majority of cases), no NTM-treating clinician discontinued OMC due to concerns of failure, with a current median OMC duration of 6.2 months. Furthermore, incidence rates of possible AEs due to OMC were relatively similar to those in the phase 3 trials for OMC and other real-world analyses of novel tetracyclines, despite much longer durations of exposure in this case series [12, 13].

An important therapeutic for NTM infections is macrolides (if susceptible), which are subject to inducible resistance via the *erm* gene and prolongation of the QTc interval [14]. Importantly, OMC is not impacted by functional *erm* gene expression and has not been shown to cause clinically significant QTc prolongation. Given the lack of some clinical laboratories performing subspeciation or *erm* gene detection (highlighted in this analysis with conduction in 58.3% and 75.0%, respectively), OMC could provide a viable oral alternative option for those clinicians and sites without the complete microbiological picture.

Tigecycline and ERV have demonstrated similar in vitro activity against isolates of *M. abscessus*; however, both antibiotics are only available in intravenous formulations and are dosed twice daily, which is not ideal for prolonged treatment courses, and are associated with significant gastrointestinal AEs. OMC is dosed once daily and has shown fewer gastrointestinal AEs than TIG or ERV (8.3% in this analysis). Importantly, reported MIC₉₀ values of ERV against *M. abscessus* (1 mcg/mL) are higher than the current FDA breakpoint for *Enterobacterales*, while reported MIC₉₀ values for OMC against *M. abscessus* have been reported to be 2-fold lower than their current FDA breakpoint [5, 9].

This report has obvious limitations. First, this was a retrospective, observational case series with a small number of patients and the possibility of selection bias. Inclusion criteria for our analysis required relatively short durations of OMC exposure and follow-up (≥ 3 months) relative to traditional treatment durations associated with *M. abscessus*; therefore, although the median duration of OMC was 6.2 months, the duration of OMC exposure as it relates to outcomes may have been inadequate to detect a more (or less) favorable response. We included both pulmonary and extrapulmonary cases of NTM infection, the outcomes of which may be difficult to compare directly based on potential differences in nonpharmacological management (eg, removal of device in extrapulmonary cases). Also, subspeciation and functional *erm* gene detection were not available in all cases. However,

given the rarity of this disease, these data reflect pragmatic outcomes that can be useful for clinicians with limited to no options for *M. abscessus* treatment, even without the full microbiologic picture. Next, all patients were on ≥ 2 additional antimicrobials; therefore, analysis of the direct response of OMC is difficult. However, this is also the case with any antimicrobial used within a combination regimen. Given the multicenter analysis of our study and the complexities of performing in vitro susceptibility with novel antimicrobials, we were unable to perform MIC testing for OMC on the majority of the clinical *M. abscessus* isolates to determine initial susceptibility, and the possibility of development of OMC resistance while on therapy remains.

Despite these limitations, this is the largest real-world observational description reporting the experience of early treatment with OMC for *M. abscessus* within multiple infectious sites. A ≥ 3 -month follow-up evaluating OMC therapy by NTM-treating clinicians was required for inclusion in this analysis, which is a strength compared with other retrospective observational studies. Also, OMC was studied in some patients who had been treated with numerous antibiotics without success over long intervals of time. Finally, although MICs for OMC were only reported in 8.3% of isolates, MICs for TIG were reported in 91.7% of isolates, and previous reports have shown a high correlation between the 2 antibiotics for *M. abscessus* [5, 6]. While these early experiences with OMC for *M. abscessus* are important to document, prospective studies and larger real-world analyses are urgently needed for these difficult-to-treat infections.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Patient consent. This study does not include factors necessitating patient consent. Furthermore, the design of the work has been approved by local ethical committees.

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