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MAJOR ARTICLE

Long-term Safety and Tolerability of Omadacycline for the Treatment of *Mycobacterium abscessus* Infections

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Background. *Mycobacterium abscessus* is a virulent human pathogen. Treatment is complex and often poorly tolerated with suboptimal rates of eradication, highlighting the need for improved therapeutics. This study reports clinical experience with omadacycline for treatment of *M abscessus* infections at five large nontuberculous mycobacterial (NTM) disease clinics across the United States to better understand long-term safety and tolerability.

Methods. We conducted a multicenter retrospective chart review of adults with *M abscessus* infections. All patients treated with omadacycline as part of a multidrug therapeutic regimen through December 2021 were included. Clinical data from time of omadacycline initiation and up to 12 months of follow-up were collected. Descriptive statistics were performed.

Results. Analysis included 117 patients. Among patients with *M abscessus* isolate subspeciation, 58 of 71 (81.7%) were *M abscessus* spp *abscessus*. In isolates with reported drug susceptibility testing, 15 of 70 (21.4%) had confirmed susceptibility to macrolides. The most common site of infection was lungs. Median duration omadacycline treatment was 8 months (range, 0.25–33 months; interquartile range, 4–15 months). Omadacycline was discontinued in 60 patients (51.3%); 20 completed planned treatment course, 23 experienced intolerance or adverse event leading to drug cessation, and 17 stopped due to cost, death (unrelated to NTM infection or therapy), or another reason. In those with pulmonary disease, 44 of 95 (46%) had 1 or more negative cultures at time of final microbiological assessment, with 17 of 95 (18%) achieving culture conversion.

Conclusions. This study reports data supporting long-term safety and tolerability of omadacycline along with signal of effectiveness in treatment of *M abscessus* infections.

Keywords. antibiotic; *Mycobacterium abscessus*; nontuberculous mycobacteria; NTM.

Mycobacterium abscessus is a virulent human pathogen causing pulmonary and other infections [1]. Despite guidelines-based recommendations describing antimicrobial regimens for the treatment of these infections, *M abscessus* infections are difficult to cure because of pathogen-specific inherent and mutational resistance mechanisms, few available antimicrobials with proven in vitro and in vivo efficacy, and suboptimal host tolerance of the prolonged combination antimicrobial treatment regimens [1, 2]. Most of the antimicrobials with known in vitro activity against *M abscessus* do not have oral formulations [2]. Thus, there is an unmet need for accessible therapeutics that are efficacious, safe, and tolerable for patients with these difficult-to-treat infections.

Omadacycline is an aminomethylcycline antimicrobial that has promise as a component of antimicrobial regimens directed against *M abscessus*. Structurally similar to both doxycycline and tigecycline, this semi-synthetic tetracycline derivative has a broader spectrum of antimicrobial activity due to modified side chains [3]. Initially approved by the United States (US) Food and Drug Administration in 2018 for the treatment of community-acquired bacterial pneumonia and skin and soft tissue infections (SSTIs) [4–7], omadacycline has in vitro activity against several rapidly growing mycobacteria species including *M abscessus*, with bactericidal effect similar to that of tigecycline [8–11]. Omadacycline is available in both oral and intravenous formulations and has a favorable safety profile for its labeled indications; however, these treatment courses typically do not exceed 14 days and longer-term safety and efficacy data are not available [7].

Although there is increasing off-label use of omadacycline for *M abscessus* infections, the current literature is limited to case reports and small case series [12–14]. There is a paucity of data demonstrating its efficacy and tolerability with extended

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durations of treatment and in large numbers of patients. We aimed to expand upon current knowledge by reporting the clinical experience of the use of omadacycline in the treatment of both pulmonary and extrapulmonary *M abscessus* infections in a cohort of patients from several large centers specializing in the treatment of nontuberculous mycobacteria (NTM) infections across the US with special interest in assessing longer-term safety and tolerability data in a heterogenous real-world sample.

METHODS

Data were abstracted from medical records review of adult patients attending clinics specializing in treatment of NTM at all sites. Each clinic searched its own clinical databases to identify omadacycline prescription. Patients with culture-confirmed diagnosis of *M abscessus* infection with omadacycline administered as a component of an antimicrobial treatment regimen were identified. Data available through 31 December 2021 were included. Study data were collected and managed using Research Electronic Data Capture (REDCap) tools hosted at the Medical University of South Carolina (MUSC) [15, 16].

Routinely obtained clinical data from the time of omadacycline initiation and up to 12 months following omadacycline initiation were included in the analysis. Baseline data included demographics, medical history, and NTM history including key radiographic and microbiologic features. Follow-up case report forms collected interval information about patient-reported side effects, results of any studies performed for safety monitoring, microbiologic and radiographic data, and an overall clinician assessment of the patient's global health status (ie, improved, unchanged, or worse). A comprehensive list of collected variables is presented in Supplementary Table 1. Relationships of reported adverse effects to omadacycline were determined by treating provider. For patients with *M abscessus* pulmonary disease, we defined culture conversion as two consecutive negative cultures and no subsequent positive cultures; a patient with only one negative culture with no subsequent cultures was deemed not to have achieved culture conversion. Cultures for these patients were collected via spontaneous expectoration, sputum induction, or bronchoscopy with bronchoalveolar lavage. Inability to obtain culture data following initiation of treatment did not equate with therapeutic success. Refractory disease was defined as persistently positive cultures despite six months of appropriate antimicrobial therapy. Data were analyzed in aggregate and descriptive statistics were performed.

This project was reviewed by the institutional review boards at all participating sites (MUSC, National Institutes of Health, National Jewish Health, New York University, and Oregon Health & Science University) and determined that the study was exempt from human research subject regulations.

RESULTS

Participants and *M abscessus* Disease Characteristics

Records from 117 patients were abstracted from the five participating sites. Geographic distribution of patients was wide, with most residing in close proximity to the participating centers (Supplementary Figure 1). Overall, 65% (76/117) of patients were female and 82% (96/117) were White. The site of mycobacterial infection varied, with 80% (94/117) having only pulmonary infection. Extrapulmonary infections included SSTI (10%), peritonitis (3%), bone and joint (1%), and disseminated (1%). A small portion (5%) of patients were reported as having multiple sites of infection (eg, bone and joint plus SSTI). A total of 8% of infections were determined to be related to a surgical site or procedure. Complete baseline demographics at the start of omadacycline therapy are reported in Table 1.

For the patients with NTM pulmonary disease, the underlying pulmonary disease was non–cystic fibrosis bronchiectasis (69%), cystic fibrosis (24%), sarcoidosis (5%), and other interstitial lung diseases (6%) including pulmonary fibrosis, interstitial pneumonitis, cryptogenic organizing pneumonia, obliterative bronchiolitis, and cystic fibrosis transmembrane conductance regulator dysfunction syndrome. Bronchiectasis (92%) and nodules (87%) were the most common radiographic features described. Cavities were present in 23% of patients. Notable additional medical history is reported in Table 1.

Mycobacterium abscessus subspeciation was determined for 60% (71/117) of isolates; among these isolates, 81.7% (58/71) were *M abscessus* subspp *abscessus*. Comprehensive macrolide susceptibility testing results were available for 60% (70/117) of isolates, among which 78.6% (55/70) had confirmed inducible macrolide resistance and only 21.4% (15/70) were susceptible (Table 2). Among the 80 isolates for which tigecycline minimum inhibitory concentration (MIC) was available, median MIC was 1 (range, 0.06–4) μg/mL (Table 2). Complete distributions of MICs for tigecycline and amikacin are reported in Supplementary Figure 2.

Omadacycline Exposure

Omadacycline was initiated as a component of initial antimicrobial therapy in 11% (13/117) or as a stepdown after initial intravenous antimicrobial therapy in 46% (54/117) patients (Table 3). Rationales for later initiation of omadacycline included addition of omadacycline to the regimen for the treatment of refractory disease (32% [37/117] of patients) and/or replacement of other antibiotics that were stopped for reasons of intolerance or safety (24% [28/117]). In all patients, omadacycline was administered as a component of combination antimicrobial treatment. In patients on omadacycline, the median number of concomitantly administered antimicrobials was 3 (range, 2–6); the number of different antibiotic combinations was large (Supplementary Figure 3). The median duration of

Table 1. Baseline Demographics at the Start of Omadacycline Treatment

Characteristic	No. (%)
Total No. of subjects	117
Age, y, mean ± SD	55.1 ± 18.9
Female sex	76 (65)
Race/ethnicity	
White	96 (82)
African American	4 (3.4)
Asian	12 (10)
Non-white Hispanic	3 (2.6)
Other	2 (2)
Insurance coverage (n = 93[a])	
Private	49 (53)
Medicare	39 (42)
Medicaid	4 (4)
Other	1 (1)
BMI, kg/m^2, mean ± SD	21.7 ± 4.4
FEV_1 (% predicted), mean ± SD (n = 71)	69.74 ± 20.9
Tobacco history (n = 95[b])	
Current	0 (0)
Former	28 (29)
Never	67 (71)
Primary classification of infection site	
Pulmonary	94 (80)
Skin and soft tissue	12 (10)
Multiple sites of infection[c]	6 (5)
Peritonitis	3 (3)
Disseminated[d]	1 (1)
Bone/joint	1 (1)
Other medical condition	
Gastroesophageal reflux disease	59 (50.4)
Depression/anxiety	30 (25.6)
Diabetes mellitus	15 (12.8)
Connective tissue disease	12 (10.3)
Immunodeficiency[e]	11 (9.4)
Transplant recipient[f]	10 (8.5)
Chronic kidney disease	10 (8.5)
Active malignancy	8 (6.8)

Data are presented as No. (%) unless otherwise indicated. There were 117 subjects included in the overall dataset, but denominators for categories with missing data are acknowledged accordingly.

Abbreviations: BMI, body mass index; FEV_1, forced expiratory volume in 1 second; SD, standard deviation.

[a]Total number of participants is reduced as 1 participating site did not have access to patient insurance status.

[b]Tobacco use history was only recorded for patients with diagnosis of nontuberculous pulmonary disease.

[c]Multiple sites of infection include involvement of >1 of the following sites in any combination: pulmonary, bone and joint, and/or skin and soft tissue.

[d]The infection considered to be disseminated involved multiple extrapulmonary lymph nodes.

[e]This was reported as hypogammaglobulinemia in 2 patients and no further data were provided for others.

[f]Transplant type: lung (n = 6), kidney (n = 2), stem cell transplant (n = 2).

Table 2. Microbiologic Data—*Mycobacterium Abscessus* Isolates

Subspecies and Susceptibility	No. (%)
Subspecies of *Mycobacterium abscessus* (N = 117)	
abscessus	58 (49.6)
massiliense	11 (9.4)
bolletii	2 (1.7)
Not identified	46 (39.3)
Susceptibility to macrolides	
Confirmed susceptibility to macrolide	15 (21.4)
Inducible macrolide resistance present	55 (78.6)
Susceptibility to other key antimicrobials, MIC, median (range)	
Susceptibility to amikacin	16 (2–64)
Susceptibility to tigecycline	1 (0.06–4)

Data are presented as No. (%) unless otherwise indicated. Subspecies identification and reported susceptibility to macrolides (n = 70), amikacin (n = 85), and tigecycline (n = 80) are reported for subjects in whom data were available.

Abbreviation: MIC, minimum inhibitory concentration.

treatment with omadacycline was 8 months (range, 0.25–33 months; interquartile range, 4 –15 months). Most were treated with a dose of 300 mg daily, although 4 patients were treated with a modified dose (150 mg daily) to try to mitigate refractory nausea. Therapy was discontinued in 60 patients, of whom 20 (17.1% of total) completed a planned course of therapy. The remaining 57 patients (48.7% of total) were still on the treatment regimen at the time of data abstraction (Table 3). Treatment decisions including initiation of omadacycline, use of concomitant antimicrobials, dose modification, and cessation of therapy were determined by individual providers at each site.

Adverse Events

Adverse events were reported in 46 patients (39.3%) (Table 4). Adverse events that were directly attributed to omadacycline were reported in 35 patients (29.9%), and 23 patients (19.7%) stopped therapy because of adverse events. Duration of therapy until time of discontinuation of omadacycline for any adverse event varied, with average duration of therapy prior to drug cessation being 5.7 months (median, 3 [range, 0.25–25] months). The most frequently reported adverse event was nausea with or without emesis, occurring in 21.4% of patients, and this was identified in most patients within 2 months of treatment initiation. Adverse events resulting in discontinuation of omadacycline included nausea (n = 13), abnormal hepatic function (n = 2), rash (n = 2), anemia (n = 2), eosinophilia (n = 1), leukopenia (n = 1), esophagitis (n = 1), diarrhea (n = 1), and weight loss (n = 1). All except weight loss were directly attributed to omadacycline as per determination of the treating clinician. Abnormal serum liver chemistries and eosinophilia leading to omadacycline cessation were reported in the same subject.

Efficacy

In patients with *M abscessus* pulmonary disease, a total of 44/95 patients (46%) had 1 or more negative cultures at the time of their final microbiological assessment, with 18% (17/95) meeting definition of culture conversion. As previously stated, 31 patients were identified as having refractory *M abscessus* pulmonary disease as indication for initiation of omadacycline

Table 3. Omadacycline History

Characteristic	No. (%)
Duration of treatment, mo	
Median	8
Range	0.25–33
Interquartile range	4–15
Dose of omadacycline	
150 mg daily	4 (3.4)
300 mg daily	112 (95.7)
Unspecified	1 (<1)
Rationale for use of omadacycline[a]	
Initial therapy	13 (11.1)
Transition from intravenous therapy	54 (46.2)
Addition to regimen for treatment of refractory disease	37 (31.6)
Intolerance to other NTM therapy	28 (23.9)
Patients who discontinued therapy during study period	60 (51.3)
Reason for discontinuation, No. (% of total treated, N = 117)	
Completion of planned therapy	20 (17.1)
Adverse event or intolerance	23 (19.7)
Cost	7 (6.0)
Death (not related to NTM infection or treatment)	4 (3.4)
Other[b]	6 (5.1)

Data are presented as No. (%) unless otherwise indicated. Data are inclusive of those who stopped treatment as well as those who were on active treatment at the time of data extraction.

Abbreviation: NTM, nontuberculous mycobacteria.

[a]Some patients with multiple/overlapping indications for omadacycline therapy.

[b]Included the following: pregnancy (n = 1), growth of *Mycobacterium avium* complex (n = 1), resumption of intravenous therapy (n = 1), unknown (n = 2), discontinued due to development of inducible macrolide resistance so as to avoid antimicrobial monotherapy (n = 1).

Table 4. Adverse Events

Adverse Event	No. (%)
Any reported AE during study period	46 (39.3)
AE directly attributed to omadacycline	35 (29.9)
AE present but relation to omadacycline unknown	9 (7.7)
AE present but not related to omadacycline	2 (1.7)
AEs attributed to omadacycline[a]	
Nausea with or without vomiting	25 (21.4)
Abnormal hepatic function (transaminitis[b] or hyperbilirubinemia)	3 (2.6)
Anemia	2 (1.7)
Headache	2 (1.7)
Rash	2 (1.7)
Diarrhea	1 (<1)
Dizziness	1 (<1)
Eosinophilia	1 (<1)
Esophagitis	1 (<1)
Leukopenia	1 (<1)
Thrombocytopenia	1 (<1)
Visual changes (blurred vision)	1 (<1)
AEs not attributed to omadacycline	
Nausea	4 (3.4)
Other gastrointestinal intolerance, not otherwise specified	3 (2.6)
Weight loss	2 (1.7)
Diarrhea	1 (<1)
Headache	1 (<1)
Heartburn	1 (<1)
Hyperkalemia	1 (<1)
Memory issues	1 (<1)
Weakness	1 (<1)

Abbreviation: AE, adverse event.

[a]Some patients had >1 AE attributable to omadacycline.

[b]Transaminitis defined as aspartate aminotransferase or alanine aminotransferase >3 times the upper limit of normal.

therapy. Of those with refractory pulmonary disease, 13/31 (42%) had 1 or more negative cultures at the time of their final microbiologic assessment, with 7/31 (23%) meeting definition of culture conversion. In those patients treated with modified dosing schedule (ie, lower dose), sputum cultures remained positive at follow-up assessment. Twenty patients (15 pulmonary, 3 SSTI, and 2 peritonitis; 17.7% of total) had therapy stopped as planned, suggesting there was not likely refractory disease (ie, persistent infection). Data from the clinician's global assessment of patient status at each encounter were available for 108 patients. The rating at the final encounter (including those still on therapy) was better for 69 patients (63.8%), unchanged for 29 patients (28.9%), and worse for 10 patients (9.3%). The rating at the final encounter for the 20 patients who had therapy stopped as planned was better for 16 patients (80%), unchanged for 2 patients (10%), and worse for 2 patients (10%).

DISCUSSION

Our report summarizes the real-world clinical experience of the use of omadacycline, in combination with other antimicrobials, for the treatment of *M abscessus* infections at five NTM centers across the US. To our knowledge, this is the largest cohort assembled to date, with the most detailed longitudinal safety and tolerability information.

There are two key findings from our study. First, omadacycline administered in combination with other antimicrobials was relatively safe over a median duration of eight months. Three people had treatment-limiting transaminitis and/or hyperbilirubinemia, and hematologic abnormalities including leukopenia, eosinophilia, anemia, or thrombocytopenia occurred in five people. While none of these laboratory abnormalities were determined to be life threatening, these findings support the need for periodic routine testing of blood counts and serum chemistries. Pancreatitis has been reported as a rare class effect of tetracycline antibiotics and reported in post-marketing surveillance of tigecycline [17]; however, there were no episodes of pancreatitis reported in our study population. As has been reported by others, nausea was common, occurring in about one-fifth of cohort patients [18]. Efforts to mitigate the nausea, including pretreatment with anti-emetic medications and omadacycline dose modification, were modestly successful as 7 of the 29 patients (24%) reported to have nausea were able to remain on omadacycline therapy.

The demonstration of longer-term safety and tolerability of omadacycline is an important addition to our knowledge base. The treatment of *M abscessus* infections typically involves much longer durations than used for the treatment of community-acquired pneumonia and SSTIs, from which the majority of safety data on omadacycline has been derived [4–6]. The duration of omadacycline treatment for these approved indications is typically 7–14 days [5, 6], whereas we are reporting safety and tolerability data for a median treatment duration of eight months. Furthermore, the adverse events profile in our study are similar to what has been reported in the literature for shorter durations, consisting of mainly nausea with or without emesis [5, 6, 18], but there was not an increase in adverse events with longer treatment exposure.

A second important finding is that of potentially promising effectiveness of omadacycline-containing regimens in this cohort of patients with a high prevalence of macrolide resistance. We can infer assessments of treatment effectiveness through a few variables captured from the medical records but are cautious about inferences regarding omadacycline's effectiveness since this retrospective observational study lacked randomization, a comparator regimen, and blinding, and because omadacycline was not used as monotherapy but rather always in combination with a variety of other antimicrobials and/or with nonantimicrobial therapies known to address other aspects of bronchiectasis. Findings suggestive of clinical benefit include completion of a treatment course (ie, presuming clinical cure) in approximately 18% of patients, a high rate of clinical improvement as assessed by treating clinicians, and encouraging microbiological results in the patients with NTM pulmonary disease. For the latter, nearly 50% had their final sputum culture negative for *M abscessus*. Using a stricter definition for culture conversion (ie, two consecutive negative cultures), 18% achieved this goal, but we are limited by the number of available cultures and note that a large proportion (~50%) of the patients were still on therapy at the time of data analysis. We also note that many subjects met the definition of refractory disease, and of these subjects 42% had their final culture negative and 23% met the definition of culture conversion. Given the limitations, we believe this compares favorably to a reported *M abscessus* spp *abscessus* (the most common pathogen) culture conversion rate of approximately 35% from a systematic review of the literature [19]. It is additionally notable that most of the *M abscessus* in this cohort was subspecies *abscessus*. Other reports have also identified this as the most common subspecies involved in *M abscessus* infections (both pulmonary and extrapulmonary) [20–22]. *Mycobacterium abscessus* subspp *abscessus* tends to have resistance mechanisms (eg, presence of intact *erm* gene) that reduce the number of therapeutic options [1].

We acknowledge there are limitations to susceptibility testing of antibiotics against NTM, in part because of the slow growth of the pathogens and the degradation of drug in solution with time [23]. It will be important to validate an assay that can assess omadacycline susceptibility for broader clinical use. Nonetheless, omadacycline has been shown to be at least as potent as tigecycline in in vitro testing for MICs [3, 24]. Although susceptibility breakpoints for tigecycline have not been determined for *M abscessus* infections, we can hypothesize that it should have had activity against the pathogens treated in our subjects based on the reported MICs for those tested [25]. Since omadacycline has similar pharmacokinetic parameters as tigecycline, we can infer that it should have activity against these pathogens as well [3, 9, 24]. Based on these predictions and our findings, these results support further investigation of omadacycline for the treatment of *M abscessus* infections, both pulmonary and extrapulmonary.

There are several limitations to the study, most of which are typical of retrospective data collections and reflective of clinical practice; there was variance in practice patterns (eg, frequency of clinic visits and microbiologic testing, standardization of treatment regimens), and some of the treatment occurred during the pandemic, resulting in some visits conducted through telehealth. As such there is also variance in the amount of data available for all subjects. Additionally, full microbiologic identification (ie, subspecies) and drug susceptibility profiles, specifically for macrolides, were not reported for each isolate. We also raise attention to the patients who had to stop therapy because of cost; this barrier to treatment with omadacycline limits the number of patients with *M abscessus* infections that could have been included in this analysis and thus we will not know what their outcomes might have been had the drug been more accessible. We are optimistic that the data reported here will provide the additional evidence to support increased access to this important antimicrobial.

However, there are also strengths to this analysis. Ours consists of a much larger and diverse patient sample with a wider range of treatment indications. In contrast to previously published case series reporting the use of omadacycline in the treatment of *M abscessus* pulmonary infections, we included all individuals who were prescribed therapy, not only those who were on treatment for a several-month course [12–14]. We believed this would provide greater generalizability with respect to tolerability and adverse events associated with longer-term treatment, especially since omadacycline is used for extrapulmonary infections as well.

In conclusion, this real-world assessment of omadacycline used in combination with other antimicrobials for treatment of *M abscessus* infections provides valuable information regarding its tolerability and adverse events with long-term exposure, and also offers some inference as to its effectiveness in a difficult-to-treat infection. These observations provide evidence in support of a clinical trial to formally evaluate the

efficacy, safety, and tolerability of omadacycline for the treatment of *M abscessus* 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.

Notes

Author contributions. C. M. M., K. L. W., and P. A. F. conceived and designed the study, analyzed data, and wrote the manuscript. W. B., P. E. F., A. L., G. P., R. S., and C. D. V. collected data and edited the manuscript. D. A.-H., C. L. D., K. N. O., and S. E. D. analyzed data and edited the manuscript.

Patient consent. This study was determined to be exempt from human subjects research regulations and thus does not include factors necessitating patient consent. The design of the work was approved by local ethical committees at all participating sites.

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