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Case report

Omadacycline for the treatment of *Mycobacterium abscessus* infections: Case series and review of the literature

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ABSTRACT

Treatment of *Mycobacterium abscessus* infections are problematic due to inherent multidrug resistance and lack of response to antibacterials commonly used as therapy for other mycobacterial infections. We report the clinical success of five patients who received definitive-treatment with an omadacycline-containing combination regimen for *M. abscessus* infection.

Introduction

Mycobacterium abscessus (*M. abscessus*) is an acid-fast bacillus (AFB), classified as a rapidly growing nontuberculous mycobacteria (NTM). It is the third most common NTM respiratory pathogen after *Mycobacterium avium* complex (MAC) and *Mycobacterium kansasii* in the United States and is emerging as a cause of skin and soft tissue infections. It is inherently multidrug-resistant, challenging to treat, and often does not respond well to antimicrobials commonly used for other mycobacterial infections [1,2]. While tigecycline is one of the better options currently available for combination regimens, its long-term use has been associated with severe toxic adverse effects resulting in patient dissatisfaction. Also, it is only available as an intravenous formulation [3]. Omadacycline, an aminomethylcycline derivative of the tetracycline class was approved in 2018 in the United States for the treatment of community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections. (ABSSSI) and is available as both intravenous and oral formulation [4,5]. We present five cases of *M. abscessus* infections in patients successfully treated with omadacycline therapy as part of a multidrug combination regimen.

Cases

Case 1

A 25-year-old female with a past medical history of undergoing bilateral breast silicon implants in the Dominican Republic two months prior to admission, presented to the hospital with a one-month history of right breast swelling, pain, and erythema with associated intermittent subjective fevers. She was evaluated in a breast clinic, and magnetic resonance imaging (MRI) of the right breast was performed, revealing a large peri-implant effusion with debris. The patient was subsequently referred for an ultrasound-guided aspiration, which yielded 160 mL of "yellow-green" fluid. She was prescribed a course of amoxicillin-clavulanate and discharged home. Due to the persistence of pain and erythema, she presented to our Emergency Department (ED) five days later for further evaluation. In the ED, she was afebrile, 37.8 °C, and her heart rate was 134 beats/min. Initial physical examination demonstrated a young female in no acute distress with right breast swelling and erythema of the medial side of her right breast.

There was localized tenderness on palpation without evidence of fluctuance, drainage, or induration. The surgical incision site was well healed. Repeat ultrasound of the right breast showed persistent peri implant fluid and debris seen within all four breast quadrants. The patient underwent surgical exploration of the right breast with drainage of

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a deep abscess, washout of the right breast capsule, and removal of bilateral intact mammary implants.

The operative report described approximately 500 mL of purulent fluid from the right breast that was expressed and sent for cultures and sensitivities. Cultures from the initial aspiration and operative washout demonstrated growth of *M. abscessus/chelonae*. The patient was discharged to the hospital's outpatient parenteral antimicrobial therapy (OPAT) infusion unit to receive empiric antimicrobial therapy pending susceptibilities. Medications included azithromycin 500 mg orally (PO) daily, moxifloxacin 400 mg PO daily, tigecycline 50 mg intravenously (IV) daily, and amikacin 15 mg/kg administered intravenously on Monday, Wednesday, and Friday. The patient developed gastrointestinal side effects from the medications a few weeks into therapy. Susceptibility results demonstrated a macrolide susceptible strain [Table 1]. Moxifloxacin was discontinued due to ongoing side effects from her regimen. Omadacycline susceptibility testing was performed. Omadacycline MIC returned at 0.25 ug/mL. The patient completed approximately three months of therapy with tigecycyline IV, amikacin IV and azithromycin PO in our OPAT infusion unit and transitioned to omadacycline PO combined with azithromycin PO to complete a 6-month course.

Case 2

A 64-year-old Indian female with a left buttock wound, following an influenza vaccination administered in that area 6 months prior, presented to the hospital after a syncopal episode in her surgeon's outpatient office. Two months after injection she noticed that her left buttock became more swollen and red. She followed up with her primary care specialists, who gave her a course of oral cephalexin without improvement. The patient was subsequently referred to the hospital for computed tomography (CT) abdomen/pelvis, which showed a 3.3 × 6.7 × 9.7 cm fluid collection within the subcutaneous fat of the left buttock with no abscess in the muscle. On physical exam, there was a 7 × 5 cm eschar over an area of fluctuance with associated purulent drainage. The patient underwent excisional debridement of the left buttock abscess. Ten mL of purulent fluid was evacuated and sent for culture. A wound vac was placed, and the patient was discharged with surgical follow-up.

She returned one week later for further excisional debridement and closure of the wound. In the operating room, the patient was found to have a 7 × 3 cm wound with skin necrosis on the lateral aspect. The wound was irrigated and specimens were sent for culture. Culture grew *M. abscessus/chelonae*. The patient was amenable to transitioning care to the OPAT unit to receive empiric antimicrobial therapy pending susceptibilities. The medications included azithromycin 500 mg PO daily, levofloxacin 750 mg PO daily, tigecycyline 50 mg IV daily, and amikacin 1475 mg IV three times weekly. She was readmitted four days after hospital discharge due to GI intolerance to tigecycline therapy. Susceptibility testing revealed a macrolide susceptible strain [Table 1]. Levofloxacin was discontinued, and the patient remained on azithromycin, tigecycline, and amikacin. The patient continued to have GI intolerance on this regimen, and the decision was made to substitute omadacycline (MIC returned at 0.12 ug/mL for tigecycline). She was instructed to continue with azithromycin and PO omadacycline was added. She completed a total 6-month course of therapy with complete wound healing.

Table 1
Mycobacterium abscessus susceptibility test results. MIC values are expressed in ug/mL. S = susceptible. I = intermediate. R = resistant. ND = not done.

	Case 1	Case 2	Case 3	Case 4	Case 5
Amikacin	8 S	16 S	16 S	16 S	32 I
Cefoxitin	32 I	32 I	32 I	128 R	32 I
Ciprofloxacin	> 4 R	> 4 R	> 4 R	> 4 R	> 8 R
Clarithromycin	0.5 S	2 S	< 16 R	> 16 R	0.5 S
Doxycycline	> 16 R	> 16 R	> 16 R	> 16 R	> 16 R
Imipenem	8 I	16 I	16 I	64 R	8 I
Linezolid	16 I	32 R	32 R	32 R	16 I
Moxifloxacin	> 8 R	> 8 R	> 8 R	> 8 R	≥ 8 R
Tigecycline	0.12	0.5	1	0.5	0.5
Omadacycline	0.25	0.12	ND	ND	ND
Erm gene	ND	ND	Positive	ND	ND

Case 3

A 43-year-old female with breast cancer underwent bilateral mastectomy and breast implantation. Two months later, she developed left breast cellulitis. The initial physical exam was remarkable for left breast tenderness and swelling without active discharge or fluctuance. The patient was treated empirically with ertapenem 1 g IV daily and daptomycin 6 mg/kg IV daily for fourteen days. Due to lack of improvement, the patient underwent incision and drainage with breast implant removal. Surgical pathology demonstrated dermis with features suggestive of a ruptured cyst with micro abscess formation. The patient was administered ertapenem and daptomycin pending intra-operative cultures, which later grew *Mycobacterium abscessus*. Ertapenem and daptomycin were discontinued and the patient was received azithromycin 500 mg PO daily, tigecycyline intravenously 50 mg daily, and amikacin 10 mg/kg IV daily for 2 weeks followed by 15 mg/kg 3 times per week thereafter. Ten weeks into treatment, patient demonstrated significant clinical improvement, and the regimen was changed to all-oral antibiotics, including omadacycline 450 mg PO daily for 2 days followed by 300 mg PO twice daily and azithromycin 500 mg PO daily. Later susceptibility testing demonstrated inducible resistance to macrolides due to the presence of the erm gene [Table 1]. Given the significant clinical improvement, decision was made to complete therapy with the current regimen, (azithromycin and omadacycline). The patient completed a total of 24 weeks of therapy and experienced complete resolution of infection.

Case 4

A 60-year-old Korean female had a prior history of pulmonary *M. abscessus*, treated with ciprofloxacin and clarithromycin for six months. She presented to the infectious disease clinic for chronic productive cough and dyspnea. CT chest demonstrated bilateral bronchiectasis and scattered nodular opacities. Sputum cultures revealed *Mycobacterium chelonae/abscessus*. The patient was empirically administered moxifloxacin 400 mg PO daily, azithromycin 250 mg PO daily, amikacin 15 mg/kg IV daily, and tigecycline 50 mg IV daily. Four months into the treatment course, patient developed significant hearing loss, and amikacin IV was switched to amikacin nebulizer 300 mg *via* inhalation twice daily. Later, the patient developed worsening nausea and poor appetite and refused to continue treatment. She completed five months of therapy with significant improvement in cough and dyspnea. At this time, sputum cultures were still positive for growth and imaging was consistent with persistent bronchiectasis and nodular lesions. She was monitored closely in the infectious disease clinic for relapse or worsening symptoms. She was administered azithromycin 250 mg PO 3 times weekly for lifelong suppression after discussion with her care team. Later, patient reported worsening cough, dyspnea, appetite loss, and unintentional weight loss. Sputum culture was again positive for *M. chelonae /abscessus*. Imaging demonstrated bilateral bronchiectasis and patchy airspace disease. She was administered omadacycline 150 mg PO twice daily and bedaqualine 100 mg PO daily. Susceptibility testing revealed resistance to macrolides and moxifloxacin [Table 1]. The patient was continued on omadacycline and bedaqualine to complete one-year post sputum conversion. Although nine months into the ongoing treatment, microbiological and radiological response was lacking, she had significant clinical response without any adverse effects.

Case 5

A 60-year-old female underwent facial cosmetic injections with deoxycholic acid, threads procedure, and lower face elevation. One month later, she developed intermittent fevers, facial pain, and areas of swelling in the face and neck. The patient was treated with steroids and was administered four different outpatient antibiotic courses without success. The patient was evaluated by an infectious disease specialist, who obtained a microbiologic sample from one of the facial lesions, which demonstrated growth of *Mycobacterium abscessus*. The patient was referred to our hospital for further management. History revealed a new-onset productive cough. Physical examination was remarkable for multiple nodular, erythematous, non-fluctuant facial and neck lesions. CT chest showed bilateral lower lobe bronchiectasis and right upper lobe 2–3 mm nodular opacity concerning for disseminated disease. Sputum evaluation for mycobacteria was negative. The patient received amikacin 7.5 mg/kg IV single dose, followed by 5 mg/kg IV daily, azithromycin 500 mg PO daily, and tigecycline 100 mg IV single dose, followed by 50 mg IV daily. Two months into her treatment course, culture results demonstrated macrolide susceptibility with elevated amikacin MIC [Table 1]. Amikacin was discontinued, and the regimen was switched to omadacycline 150 mg PO twice daily and azithromycin 500 mg PO daily. The patient completed a total of five months of therapy with significant improvement in skin lesions and is closely followed up in our infectious disease clinic.

Discussion

We report the clinical success of five patients who received definitive-treatment with an omadacycline-containing combination regimen for *M. abscessus* infection. Our experience is similar to that previously reported. Pearson et al. described a case series of four patients with microbiologically confirmed *M. abscessus* cutaneous (n = 2), pulmonary (n = 1), and osteomyelitis (n = 1) infections treated with omadacycline-containing combination regimens. Three of four patients demonstrated clinical success with one patient discontinuing therapy at 6 months due to suspected omadcycline-induced nausea and vomiting. All patients received oral omadacycline 300 mg daily, two of whom received a loading dose of 450 mg daily for the initial 2 days. The median omadacycline duration was 166 days: (range, 104–227 days) [6]. Minhas et al. reported clinical success with oral omadacycline 150 mg daily for pulmonary *M. abscessus* given in combination with amikacin and aztreonam for 4 months [7]. Morrisette et al. reported experience with 12 patients, 75 % of whom achieved clinical success. The majority of patients had pulmonary infections (n = 7), followed by bone/joint (n = 2), abdominal (n = 1), cutaneous (n = 1) and bloodstream (n = 1). Median time to initiation of omadacycline was 4.7 months. Tigecycline MIC was used as a surrogate for omadacycline in 11 of the 12 isolates. All patients received oral omadacycline dosed at 450 mg PO daily for 2 days, followed by 300 mg PO daily thereafter, in addition to at least one additional antimicrobial agent. Median duration of omadacycline treatment was 6.2 months. Three patients experienced adverse events, though none required permanent discontinuation. One experienced nausea/vomiting and the dose was reduced to 150 mg PO daily with resolution, one experienced AKI which resolved after temporary discontinuation of administration and one experienced transient liver enzyme elevations to $\geq$ 3 times upper limit of normal [8].

M. abscessus accounts for approximately 80 % of all the infections caused by rapidly growing mycobacteria. *M. abscessus* was first described by Moore and Frerichs in 1953 and was isolated from a woman with chronic osteoarthritis. She had developed a gluteal abscess that yielded mycobacteria species, and thus, the species was termed 'abscessus' [9]. *M. abscessus* is well known to cause skin, soft tissue, and invasive pulmonary infections. It can be seen in post-injection abscesses and wound infections following surgeries [2]. *M. abscessus* infections present a multitude of quandaries to clinicians, including accurate diagnosis, delayed availability of microbiological data, intrinsic multidrug resistance, need for timely surgical intervention and source control, need for prolonged administration of combination drug regimens, and associated adverse effects of treatment regimens. Though several agents demonstrate *in vitro* activity and have been used in various combinations, clinical success and outcomes have not been consistent.

The American Thoracic Society and Infectious Diseases Society of America recommend surgical resection and a multidrug regimen (guided by *in vitro* susceptibility) of at least three active antimicrobials in macrolide-susceptible disease and at least a 4-drug combination in macrolide-resistant disease during the initial phase when bacterial burden is most significant [10]. Regimens including amikacin, imipenem-cilastatin, linezolid, and tigecycline have been associated with increased treatment success. However, the optimal combination regimen, dosing and duration are not well established. Adverse drug effects are common due to long-term, combination antibiotic therapy, leading to frequent dosage adjustment or discontinuation [2]. In our case series, one out of 5 patients developed antimicrobial-related toxicity resulting in premature treatment discontinuation and relapse in a few years.

Various retrospective studies suggest the continuation of treatment for at least 12 months beyond sputum culture conversion for pulmonary disease and an additional 2–3 months after the recovery of the skin and soft tissue wounds [11]. Designs of regimens beyond the initial intravenous phase are challenging given *in vitro* resistance to most antimicrobials, including beta-lactams, rifampin, fluoroquinolones, sulfamethoxazole/trimethoprim, and clindamycin. Macrolides possess potent *in vitro* activity and are considered essential in treatment regimens if active. Macrolides are subject to inducible resistance through the erm (41) gene [12]. In our case series, four of five patients received definitive treatment with an omadacycline-azithromycin combination regimen, two had a macrolide-resistant isolates, with one positive for the inducible erm gene. Functional erm gene detection was not available in all of our cases. Despite the presence of the detectable erm gene, we continued azithromycin along with omadacycline. The patient completed almost three months of treatment by the time susceptibility results were reported. Given significant clinical improvement, the impression was that either the erm gene had not been expressed or the empiric regimen significantly lowered the inoculum allowing omadacycline to work effectively as monotherapy. In Case 3, we believe azithromycin monotherapy following the initial intravenous multidrug regimen led to clinical relapse and macrolide-resistance. The patient was then switched to omadacycline and bedaquiline with a favorable clinical response but no microbiological or radiologic response seven months into the ongoing treatment course. Bedaquiline is an ATP synthase inhibitor, currently only approved for multi drug-resistant tuberculosis. It is associated with adverse side effects including QTc prolongation, antagonism when combined with beta-lactams, and a black box warning of increased risk of all-cause mortality. The *in vitro* data is promising, but clinical data supporting the efficacy are lacking [13,14]. Other options considered were linezolid (potent *M. abscessus in vitro* activity attributed to its ability to penetrate extracellular fluids and cells) but is associated with myelosuppression limiting its long-term use [2,15].

Omadacycline susceptibility ranged from 0.12 to 0.25 ug/mL in two of our isolates. For the subsequent isolates, omadacycline was started using tigecycline as a surrogate for susceptibility (all five isolates were susceptible to tigecycline) [16–18].

Omadacycline potentiates the effect of many antimicrobials, including macrolides, linezolid, and rifabutin, against *M. abscessus*. Furthermore, synergy with macrolides was observed against both macrolide-resistant and macrolide susceptible isolates. Omadacycline demonstrated synergy with clarithromycin against 100 % of all isolates tested, with a fractional inhibitory concentration index of 0.4 and at least a 3 log cfu/mL reduction compared to single clarithromycin and omadacycline samples, respectively. Clarithromycin and bedaquiline combination also demonstrated synergy. However, combination with

amikacin, rifabutin, and cefoxitin instead showed an additive effect [19]. Similar findings were reported by Nicklas et al. demonstrating restoration of activity to macrolides in ten isolates and stability of omadacycline activity despite prolonged exposure of 4 weeks as monotherapy in an *in-vivo* model [20]. One possible mechanisms of synergy is through the structural modification at the level of ribosomes. However, further *in vitro* investigation is required.

Conclusion

We report the clinical success of 5 patients with *M. abscessus* infection. Given its favorable *in vitro* activity and synergy data, oral availability, long-term tolerability, and safety data, it is a promising agent to consider in combination for the treatment of *M. abscessus* infections. More studies are needed to confirm the optimal combination, dose, timing of initiation, duration of treatment and applicability to all sources of infection and subspecies of *M. abscessus.* Future investigations should include both *in-vitro* and *in-vivo* studies with azithromycin and omadacycline combinations for their possible synergistic effects as have been demonstrated with clarithromycin and omadacycline.

CRediT authorship contribution statement

Ayesha Siddiqa: Participated in the diagnostic process, data collection, and initial writing of the manuscript. **Shanza Khan:** Participated in the diagnostic process, data collection, and initial writing of the manuscript. **George D. Rodriguez:** Participated in the diagnostic process, data collection, and writing of the manuscript. **Carl Urban:** Writing – review & editing. **Sorana Segal-Maurer:** Writing – review & editing. **Glenn Turett:** Participated in the diagnostic process, Writing – review & editing.

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Ethical approval

All authors have agreed for authorship, read and approved the manuscript, and given consent for publication of the manuscript.

Consent

Consent to publish was not obtained since the case report does not contain any personal identifiers.

Conflicts of interest

All authors report no potential conflicts of interest.

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