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BRIEF REPORT

Real-World, Multicenter Case Series of Patients Treated with Oral Omadacycline for Resistant Gram-Negative Pathogens

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ABSTRACT

Introduction: Antibiotic-resistant Gram-negative bacteria have been associated with substantial morbidity and mortality and have limited treatment options available. Omadacycline (OMC) is an aminomethylcycline antibiotic that has been shown to exhibit broad in vitro activity against antibiotic-resistant Gram-negative bacteria. Given the lack of real-world data, the primary objective of our report was to describe early experience with OMC for the treatment of resistant Gram-negative infections.

Methods: This was a real-world, multicenter, observational cases series/pilot study conducted

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in the USA. Inclusion criteria included any adult patient aged ≥ 18 years who received OMC for ≥ 72 h either in the inpatient and/or outpatient setting. Clinical success was defined as a composite of 90-day survival from initiation of OMC, lack of alteration in treatment/addition of other antibiotic due to concerns of OMC failure, and lack of microbiologic recurrence within 30 days from the end of therapy.

Results: Oral OMC was used in nine cases primarily for multidrug-resistant (MDR)/extensively drug-resistant (XDR) Gram-negative bacterial infections (55.6% XDR and/or carbapenem-resistant *Acinetobacter baumannii* [CRAB]). The majority of infections were of bone/joint (55.6%) origin, followed by intra-abdominal (33.3%) origin. Clinical success occurred in 66.7% of cases, with 80.0% success each in infections of bone/joint origin or those caused by CRAB. One patient experienced an adverse effect that was not treatment limiting while on therapy (gastrointestinal).

Conclusion: The use of oral OMC in MDR/XDR Gram-negative infections exhibited a relatively high success rate with minimal adverse effects. Real-world studies with larger case numbers are needed to confirm our initial findings.

Keywords: Carbapenem-resistant *Acinetobacter baumannii*; Carbapenem-resistant *Enterobacteriaceae*; Gram-negative resistance; Omadacycline

Key Summary Points

Why carry out this study?

Antibiotic-resistant Gram-negative pathogens lead to morbidity and mortality, and available treatment options in an oral formulation are limited.

The primary objective of our report was to describe early experience with omadacycline (OMC) for the treatment of multidrug-resistant (MDR) and extensively drug-resistant (XDR) Gram-negative infections.

What was learned from the study?

Clinical success with OMC was observed in 66.7% of cases, with higher success rates in infections of bone/joint origin or those caused by carbapenem-resistant *Acinetobacter baumannii*. One patient experienced an adverse effect that was not treatment-limiting while on therapy.

The use of oral OMC in MDR/XDR Gram-negative infections exhibited a relatively high success rate with minimal adverse effects.

INTRODUCTION

The US Centers for Disease Control and Prevention (CDC) dedicate a substantial proportion of their urgent and serious threats to addressing antibiotic-resistant Gram-negative bacteria [1]. Specifically, infections caused by multidrug-resistant (MDR)/extensively drug-resistant (XDR) Gram-negative pathogens, including carbapenem-resistant *Acinetobacter baumannii* (CRAB) or *Enterobacterales* (CRE), have been associated with substantial morbidity and mortality in comparison to their susceptible phenotypes due, in part, to a lack of efficacious and safe therapies [2, 3]. Although options such as the novel intravenous (IV) beta-

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lactam/beta-lactamase inhibitors (BL/BLI), polymyxins, high-dose/extended infusion carbapenems, novel tetracycline derivatives, and/or aminoglycosides (depending on the pathogen) exist for susceptible and invasive infections, resistance to these therapies is increasing. Furthermore, various concerns have been expressed regarding some of the aforementioned antibiotics, such as minimal real-world data, tolerability issues, sub-optimal pharmacokinetics (PK) data, and/or lack of attaining pharmacodynamic (PD) targets in deep-seated infections [4, 5]. Importantly, transitions-of-care for infections caused by resistant Gram-negative pathogens are complex due to the lack of suitable alternative therapies, including those with an available oral formulation. These organisms cause chronic infections, and the lack of efficacious oral formulations for step-down therapy following initial stabilization may often lead to prolonged IV therapy, which has been shown to have its own array of complications (i.e., delayed discharge, hospital readmissions, line complications, etc.) [6, 7]. Importantly, recent randomized clinical trials have shown non-inferiority of oral agents to parenteral therapy as step-down therapy in invasive infections [8, 9]. Therefore, effective and safe antimicrobial agents, including carbapenem-sparing regimens, with in vitro activity against MDR/XDR Gram-negative pathogens with novel mechanisms of action and availability in oral formulations are urgently needed.

Omadacycline (OMC) is an aminomethylcycline antibiotic within the tetracycline class that is available in both an oral and IV formulation and not affected by common resistance mechanisms (i.e., beta-lactamases); further, it has demonstrated preserved activity against tetracycline-specific acquired mechanisms of resistance [10]. OMC has also been shown to exhibit broad in vitro activity against antibiotic-resistant Gram-negative bacteria [11, 12]. Given the lack of real-world data, the primary objective of this report was to describe early experience with OMC for the treatment of MDR/XDR Gram-negative infections.

METHODS

This was a real-world, multicenter, observational cases series/pilot study conducted at four geographically distinct academic medical centers in the USA between January 2020 and February 2021. Inclusion criteria included any adult patient aged $\geq$ 18 years who received OMC for $\geq$ 72 h either in the inpatient and/or outpatient setting. Subsequent cases in which OMC was separated by $\geq$ 60 days post-OMC discontinuation were also eligible for inclusion.

Clinical success was defined as a composite of 90-day survival from initiation of OMC, lack of alteration in treatment or addition of antibiotic to treatment due to concerns of OMC failure, and lack of microbiologic recurrence within 30 days from the end of therapy. We also aimed to describe reasons for OMC utilization and incidence of adverse effects as documented in the electronic medical record, when available.

Microbiologic recurrence was defined as a culture positive for the same pathogen as that isolated from the index culture during treatment/suppression following initial clearance of cultures. MDR isolates were defined as those showing non-susceptibility to $\geq$ 1 agent in $\geq$ 3 antibiotic categories, while XDR isolates were defined as those showing non-susceptibility to $\geq$ 1 agent in all but $\leq$ 2 antibiotic categories. A conservative approach was used to classify these organisms (e.g., if polymyxin susceptibility was not reported, MDR was chosen over XDR) [13]. Active therapy was defined as antibiotics with in vitro reported susceptibility to the isolates of which they were being targeted for, while combination therapy was defined as any antibiotic with active therapy used in tandem with OMC for $\geq$ 48 h. The Clinical and Laboratory Standards Institute (CLSI) and US Food and Drug Administration (FDA) susceptibility breakpoints were applied, when applicable, for interpretation of minimum inhibitory concentration (MIC) values [14, 15].

Descriptive statistics were utilized for analysis using IBM SPSS software, version 26.0 (SPSS IBM Corp., Armonk, NY, USA)

The study protocol was approved by the institutional review board at each participating center prior to data collection and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. This study does not include factors necessitating patient consent.

RESULTS

A total of nine cases (8 patients) met the inclusion criteria. Median (interquartile range [IQR]) age and weight were 49 (32–61) years and 77.2 (69.1–79.0) kg, respectively; 8/9 (88.9%) cases involved male patients; and 5/9 (55.6%) cases involved Caucasian patients. Common comorbidities included hemiplegia: 4/9 (44.4%), while heart failure, cerebrovascular disease, type II diabetes mellitus, and/or chronic kidney disease were documented in 2/9 cases (22.2%). No comorbidities were reported for 2/9 (22.2%) cases. The majority of patient cases had insurance coverage through Medicare (5/9 [55.6%]). All cases included in this analysis had an infectious diseases consultation, while 7/9 (77.8%) of cases had surgical interventions (e.g., debridement and/or incision and drainage).

The sources of infection were of bone/joint origin (5/9 [55.6%]), followed by infections of intra-abdominal (IAI; 3/9 [33.3%]) origin and lung (1/9 [11.1%]) origin (Table 1). The sources of osteomyelitis included vertebrae (2/5 [40.0%]), foot (2/5 [40.0%], including one patient with type 2 diabetes), and sacrum (1/5 [20.0%]). Of those with IAI, 2/3 (66.7%) had a single abscess (1 case of which also included necrotizing pancreatitis), while 1/3 (33.3%) had multiple abscesses. The last case included a patient with long-term ventilator dependence who developed ventilator-associated pneumonia (VAP). Importantly, 4/9 (44.4%) cases involved bacteremia at some point during their index infection.

A total of nine pathogens were isolated among the clinical cases in which OMC was used (6/9 [66.7%] MDR phenotype; 3/9 [33.3%] XDR phenotype). The most common pathogen isolated was CRAB (5/9 [55.6%], of which 3/5 [60.0%] were classified as XDR), followed by MDR Gram-negative isolates, including *Escherichia coli* (2/9 [22.2%]), and *Citrobacter freundii* (CRE) and *Klebsiella pneumoniae* (1/9 cases each [11.1%]). Polymicrobial cases included CRAB plus pan-susceptible *K. pneumoniae* and MDR *E. coli* plus MDR *Enterococcus faecalis* (resistant to ampicillin, vancomycin, daptomycin, and linezolid). MIC values were only determined for OMC against one isolate (*C. freundii*), and was reported as 4 mg/L. Tigecycline MICs were reported for MDR *C. freundii*, *E. coli*, and *E. faecalis* isolates, and were found to be 0.5, ≤ 1, and 0.25 mg/L, respectively. Of note, carbapenem resistance was found in the majority of the Gram-negative pathogens isolated. Other baseline and clinical criteria are shown in Table 1.

From the collection of index cultures, OMC was initiated within a median (interquartile range [IQR]) of 18.0 (9.1–29.8) days. The total median duration of OMC was 14.0 (14.0–35.0) days. The majority of cases were treated and/or suppressed with OMC strictly in the outpatient setting (7/9 [77.8%]), while 2/9 (22.2%) cases had OMC initiated in the inpatient setting and were then transitioned to continue therapy at discharge. Most commonly, OMC was utilized strictly for targeted therapy (7/9 [77.8%]), while other uses included treatment, followed by suppression (1/9 [11.1%]) or strictly suppression (1/9 [11.1%]). Oral therapy was strictly utilized in all cases, with a loading dose of 450 mg once daily on days 1 and 2 being used in 3/9 (33.3%) cases, while all patients received a maintenance dose of 300 mg once daily.

Overall, common antibiotics utilized prior to OMC initiation included aminoglycosides, carbapenems, novel BL/BLI, and/or eravacycline. Prior to OMC initiation, active antibiotic therapy against the most resistant phenotype was administered in 2/9 (22.2%) cases, for a median (IQR) of 4.0 (2.0–18.0) days. Importantly, OMC was previously used in one case from an outside hospital (clinical information not available). Active combination therapy with OMC was administered in 1/9 (11.1%) cases (VAP), which included amoxicillin/clavulanate with pan-susceptible *K. pneumoniae* and CRAB (the CRAB

Table 1 Baseline and clinical characteristics of patients treated with omadacycline for MDR/XDR Gram-negative pathogens

Subject ID	Age/sex/treatment setting	Infection source	Pathogen(s) for OMC	OMC dosage regimen	Duration of OMC (days)	Concomitant active therapy (days overlap)	90-day mortality	Alteration	Microbiologic recurrence
1[a,b]	49/male/inpatient (LOS: 34 days) + outpatient	Chronic vertebrae osteomyelitis	*XDR Acinetobacter baumannii* (CRAB)	450 mg po qd on days 1–2, then 300 mg po qd	12	None	No	No	No
2[a,b]	49/male/inpatient (LOS: 12 days) + outpatient	Chronic vertebrae osteomyelitis	XDR *A. baumannii* (CRAB)	300 mg po qd	35	None	No	No	No
3	32/male/outpatient	Chronic sacrum osteomyelitis	MDR *A. baumannii* (CRAB)	450 mg po qd on days 1–2, then 300 mg po qd	14	None	No	Yes	No
4	50/male/outpatient	Chronic foot osteomyelitis	XDR *A. baumannii* (CRAB), CoNS, *Corynebacterium* spp.	450 mg po qd on days 1–2, then 300 mg po qd	61	None	No	No	No
5	63/male/outpatient	Chronic foot bone/joint	MDR *Klebsiella pneumoniae*	300 mg po qd	14	None	No	No	No
6	26/female/outpatient	Suppression of IAI-multiple abscesses	MDR *Escherichia coli*	300 mg po qd	62	None	No	No	No
7[b]	61/male/outpatient	Treatment/suppression IAI-single abscess	MDR *Citrobacter freundii* (CRE)	300 mg po qd	9	None	Yes	Yes	No[d]
8[b]	20/male/outpatient	VAP	MDR *A. baumannii* (CRAB), pan-susceptible *K. pneumoniae*	300 mg po qd	14	Amoxicillin/clavulate (14)[c]	No	No	No
9	63/male/outpatient	IAI-single abscess/infected necrotizing pancreatitis	MDR *E. coli*, MDR *Enterococcus faecalis* (resistant to AMP, DAP, LZD, VAN)	300 mg po qd	15	None	Yes	No	No

AMP Ampicillin, *CoNS* coagulase-negative staphylococci, *CRAB* carbapenem-resistant *Acinetobacter baumannii*, *CRE* carbapenem-resistant *Enterobacterales*, *DAP* daptomycin, *IAI* intra-abdominal infection, *LZD* linezolid, *LOS* length of stay, *MDR* multidrug-resistant, *po* oral administration, *qd* once daily, *VAN* vancomycin, *VAP* ventilator-associated pneumonia, *XDR* extensively drug-resistant

[a]Same patient, different case separated by ≥ 60 days

[b]Bacteremia at some point during index infection

[c]Active therapy only for *Klebsiella pneumoniae*, not CRAB

[d]Cultures never cleared

isolate did not demonstrate in vitro susceptibility to amoxicillin/clavulanate).

Overall, clinical success occurred in 6/9 (66.7%) cases. For patients with bone/joint infections, IAI, and VAP, clinical success was observed in 4/5 (80.0%), 1/3 (33.3%), and 1/1 (100%) cases, respectively. Among the most commonly isolated pathogen (CRAB), clinical success was 4/5 (80.0%). The most common infection and isolate pair was bone/joint infections caused by CRAB, with a 3/4 (75.0%) success rate. The primary reasons for OMC utilization were due to oral availability (8/9 [88.9%]), ease of administration (7/9 [77.8%]), antimicrobial resistance to previous antibiotic(s) (5/9 [55.6%]), and/or as oral step-down therapy (4/9 [44.4%]). One patient experienced an adverse effect while on therapy that was gastrointestinal in nature; however, the adverse effect did not lead to OMC discontinuation and resolved throughout OMC continuation.

DISCUSSION

We report a case series of OMC use for MDR/XDR Gram-negative organisms in a variety of infections with an overall success rate of 66.7%. Given the dearth of oral options available for the treatment of pathogens like CRE and CRAB and OMC being documented as utilized due to its oral bioavailability and option for oral step-down therapy, the fairly high clinical success rate achieved within this case series is significant. With careful consideration to our small sample size and heterogeneity in pathogens and infection sites, OMC administered orally appears to be a promising agent for the treatment of MDR/XDR Gram-negative pathogens in certain clinical scenarios when used as part of a comprehensive antibiotic therapy regimen with infectious diseases specialist supervision and source control (when applicable).

The majority of infections and isolates for which OMC was utilized were bone/joint and CRAB, respectively, and each exhibited a success rate of 80.0%. Furthermore, clinical success was 75.0% in bone/joint infections caused by CRAB, which is higher than reported previously (approx. 40%) [16]. A common resistance mechanism in CRAB is the production of beta-lactamases (e.g., Class D, OXA-type), which do not affect the in vitro activity of OMC; therefore, OMC may represent a viable option in these clinical isolates, if proven efficacious [17]. It is also important to note that animal studies have demonstrated that OMC tissue-to-blood concentration ratios have been observed to be high in the bone mineral, which may provide a PK/PD rationale for the relatively high rates of clinical success in bone/joints infections [18]. Most reports describing real-world use of novel antimicrobials are difficult to interpret due to concomitant active combination therapy. A strength of this report is that active combination therapy was only used in 11.1% of cases and the particular concomitant antibiotic was only active against one of the two pathogens causing infection.

The three cases of failure with OMC occurred in the treatment/suppression of IAI (carbapenem-resistant *C. freundii*), treatment of chronic sacral osteomyelitis (CRAB), and treatment of IAI (MDR *E. coli,* MDR *E. faecalis*). Although all antimicrobial failures in the clinical realm cannot be fully elucidated, PK/PD data in tandem with MIC values can provide a strong framework. An MIC value for OMC was only available for the CRE isolate in the case of IAI treatment/suppression. Importantly, this patient experienced previous treatment failures (likely due to a lack of source control); this patient also failed to clear their CRE isolate and eventually had their OMC therapy altered (MIC for OMC 4 mg/L; breakpoint [FDA] for *K. pneumoniae* and *Enterobacter cloacae* only) [15]. The area under the concentration–time curve/MIC ratio has been established as the preferred PK/PD target for efficacy of tetracyclines throughout in vivo models. The 24-h static AUC/MIC values for OMC most commonly range from approximately 16 to 25 (although most commonly reported against Gram-positive organisms), which correlates with previous targets being approximately 25 for other tetracyclines [19–22]. Given the reported PK of OMC, it is possible that PD targets were not optimized in this specific case [18, 23]. Importantly, Iregui and colleagues reported variable MIC_{90} (concentration achieving 90% inhibition of isolates)

values for OMC against antibiotic-resistant *Enterobacterales* and *A. baumannii*, thereby highlighting the importance of obtaining OMC susceptibility [11]. Another case of clinical failure (sacrum osteomyelitis) lacked surgical interventions (i.e., appropriate source control), which are well-known important drivers of success. Nevertheless, the overall complexities of these cases and resistance profiles of the isolated pathogens remain apparent, with previous and concomitant active antibiotic therapy against the most resistant phenotype being administered in only 22.2% and 11.1% of cases, respectively.

The use of nearly all oral formulations of antibiotics are associated with gastrointestinal side effects. The proportion of patients in our analysis experiencing a possible gastrointestinal side effect due to OMC (11.1%) is comparable to or lower than the results of the phase 3 trials of which facilitated FDA approval, and this adverse effect resolved without discontinuation of OMC [24, 25]. The use of an oral formulation has obvious strengths, including possible reductions in hospital length of stay, infections, costs, and other complications associated with parenteral antimicrobial therapy [7].

Our study has several limitations. The small sample size and heterogeneity of patient and infection characteristics limits the external validity, this report lacked a control group which compromises our ability to interpret the clinical effectiveness and safety of OMC, and there is the possibility of selection bias. Clinical success, especially in the indications most commonly described in this report (osteomyelitis and IAI), is highly dependent on adequate source control which is difficult to critically evaluate in an observational, multicenter report with potential variations in practice and data collector interpretation. Subject ID 1 and 2 (Table 1) is composed of two cases from the same patient (cases separated by $\geq$ 60 days). It is important to note that although this patient technically met the definition of clinical success, they were re-admitted to the inpatient setting and re-started on OMC. Furthermore, OMC was often initiated after a prolonged period of time following index culture collection. Although it is impressive that nearly all patients were treated exclusively in the outpatient setting given the severity of these infections, outpatient medical records have limited details and it is possible that failures were missed if the patient went to another provider out of network. Finally, an MIC value for OMC was only available for one isolate. However, this may be due to the fact that validated antimicrobial susceptibility testing methods are often delayed following antimicrobial approvals, research use only (RUO) MTS^{TM} omadacycline strips (Liofilchem, Roseto degli Abruzzi, Italy) that were available at the time of this case series should not have been used to guide patient therapy, and the FDA-approved antimicrobial susceptibility testing devices that are available are not approved for the indications or majority of organisms within this case series. Although tigecycline MICs were reported for two additional isolates, it is challenging to predict or correlate MICs and outcomes of one tetracycline analog to another due to differences in PD profiles and in affinity for tet genes. However, it is imperative to highlight the importance of antimicrobial susceptibility testing, especially in the setting of utilizing novel agents against resistant pathogens, and such testing should be performed whenever possible.

CONCLUSIONS

This is the largest, real-world data that describes the use of oral OMC in MDR/XDR Gram-negative infections with limited-to-no other oral options, including those caused by CRAB and CRE. In addition, all cases in which OMC was used for were for infections beyond those that are currently approved by the FDA. Real-world studies with larger case numbers, comparative data, and prospective clinical trials are needed to confirm our initial findings.

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Compliance with ethics guideline. The design of the work has been approved by local institutional review boards at each participating center prior to data collection and was performed in accordance with the Helsinki Declaration of 1964 and its later amendments. This study does not include factors necessitating patient consent.

Data availabilty. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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