MAD-ID Newsletter

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MAD-ID
MAKING A DIFFERENCE IN INFECTIOUS DISEASES®

Volume 10: Issue 3

In this issue

Live, Virtual, Hybrid? How will you attend educational conferences in 2021?

The MAD-ID Planning Committee is working hard to plan the quality and camaraderie of the live annual meeting that we all enjoy. Our meeting is planned for May 19-22, 2021 at the Omni Hotel in ChampionsGate, Florida. We will communicate with you via the website, emails, and social media if anything changes or as new information is available.

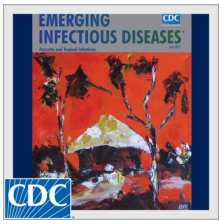
Other Infectious Diseases conferences in 2021 are planning for various hybrid and virtual models. Watch these sites for updates!

- Conference on retroviruses and opportunistic infections, March 6-10, 2021, virtual, www.croiconference.org
- SHEA Spring Conference, April 14-16, Houston, Tx, www.sheaspring.org
- ASM Microbe, June 3-7, Anaheim, California www.asm.org
- European Congress of Clinical Microbiology and Infectious Diseases, July 9-12, Vienna, Austria, www.eccmid.org
- IDWeek, September 29-October 3rd, San Diego , California, www.idweek.org

Educational Podcasts to Keep Up with the Latest in Infectious Diseases

Podcasts have emerged as a preferred way to listen to experts and colleagues discuss important new information and literature. Previous MAD-ID Faculty and Attendees have been featured on episodes of several podcasts. Share your favorite ID and medical education podcasts with MAD-ID by tagging @MAD_ID_ASP on Twitter!

Here are some ideas to get you started. Find them on your favorite streaming/podcast application.



MAD-ID CE Webinars available now!

MAD-ID held three virtual sessions featuring exceptional speakers and timely topics. The webinars are available on the MAD-ID online learning platform. After you log in, look for these sessions under the heading "MAD-ID Webinars 2020". For those who didn't catch them live, you can access the quiz and claim CE after completing the online webinars.

https://mad-idtraining.org/certification/login/index.php

Implementing the 2020 Vancomycin Guidelines: What Every Clinician Needs to Know	•Presented by Emily L. Heil, PharmD (University of Maryland Medical Center) Erin K. McCreary, PharmD (University of Pittsburgh Medical Center)
Sepsis 2020	•Presented by Edward Septimus, MD (Texas A&M Medical School) and Mary Millard, MEd (International Patient Advocate Speaker)
Guideline Updates: Community-Acquired Pneumonia and Asymptomatic Bacteriuria	•Presented by Thomas M. File, Jr., MD, MSc (Summa Health and Northeast Medical University) and Emily S. Spivak, MD, MHS (University of Utah College of Medicine)

What you should know about the Pasteur Act

The *Pioneering Antimicrobial Subscriptions to End Upsurging Resistance (*PASTEUR*) Act*, was introduced by Sen. Michael Bennet (D-CO) and Sen. Todd Young (R-IN) to support the development of new antibiotics and promote appropriate use of existing ones, helping to limit the increase and spread of resistant infections. The bill reflects recommendations promoted by many experts in infectious diseases and antibiotic resistance. It proposes creating a subscription model for critical need antimicrobials and $11 billion to support the effort over 10 years.

To read a summary of the bill's actions and see the full language of the proposed legislation, visit Senator Bennet's website: https://www.bennet.senate.gov/public/_cache/files/c/2/c2068e9f-8440-4960-86f4-acdd13145430/513C16806B1E8526E9F919EA7A72A004.pasteur-act---one-pager-1-.pdf

Please consider contacting your senators to support the PASTEUR act to confront the ongoing crisis of antibiotic resistance.

5 Ways Pharmacists Can Be Antibiotics Aware, posters now available

For Antibiotic Awareness week 2019, the Centers for Disease Control and Prevention partnered with the American Society of Health-System Pharmacists and the Society of Infectious Diseases Pharmacists to create "5 Ways Pharmacists can be Antibiotics Aware" posters. Those electronic pharmacy posters are now available for ordering (free) through the CDC's Info On Demand service.

- Go to https://wwwn.cdc.gov/pubs/cdcinfoondemand.aspx
- Search for Programs under "Antibiotic Use"
- 11 x 17 "5 Ways" posters can now be ordered. Look for the item titled *Be Antibiotic Aware | 5 Ways Hospital Pharmacists Can Be Antibiotics Aware Poster (11x17)*

BE ANTIBIOTICS AWARE
SMART USE, BEST CARE

Antibiotic Awareness Week is is Nov 18th – 24th

Omadacycline: A Versatile Agent with a Developing Niche

Continuing Education Activity

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Disclosures: Ms. Hanson and Dr. Kobic have no conflicts of interest to disclose relevant to this learning activity.

Learning Objectives:
At the end of this article, learners will be able to:

1. Recognize the mechanism of action, microbiologic activity, and common resistance patterns against omadacycline
2. Describe the pharmacokinetics/pharmacodynamics (PK/PD) of omadacycline
3. Identify prevalent adverse effects and drug interactions of omadacycline
4. Apply dosing and clinical trial results to patient cases

Disclaimer: The information contained in this newsletter is emerging and evolving because of ongoing research and is subject to the professional judgment and interpretation of the practitioner. We are not responsible for the continued currency of the information, for any errors or omissions, and/or for any consequences arising from the use of the information in any practice setting.

Overview

Tetracyclines are one of the oldest antibiotic classes to date and were originally introduced in the 1940s. Known for activity against a wide variety of pathogens, prescribing rates among outpatient physicians were higher than most common antibiotics (penicillins (PCNs), trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones (FQ's)) in the early 1990's.[1] However, clinical utility against relevant pathogens eventually diminished with emergence of tetracycline resistance. Recent efforts by industry have encouraged a new age of synthetic tetracyclines with potent *in vitro* activity against organisms that have evaded first-line options. Omadacycline's (OMC) broad spectrum range includes activity against Gram-positives, Gram-negatives, anaerobes, and atypical organisms. While clinical evidence against non-tuberculous mycobacterium (NTM) infections is sparse, OMC's potential in this space has prompted interest, particularly in the treatment of NTM species *Mycobacterium abscessus* infections.[2]

Introduction

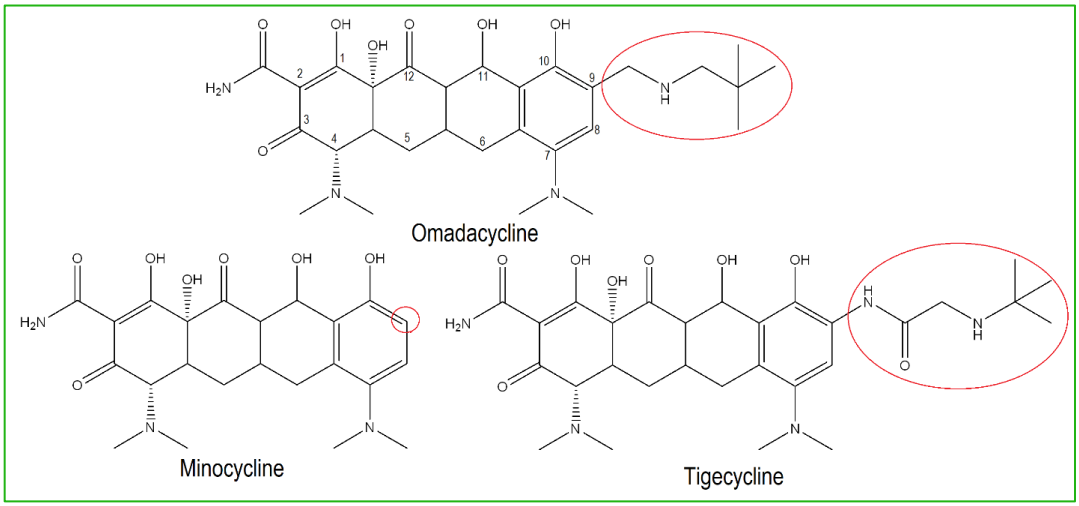
Since the approval of minocycline in 1971, OMC is the first intravenous (IV) and oral (PO) available tetracycline to come to market.[3] OMC is a new aminomethylcycline (AMC) (tetracycline derivative) antibiotic that can be administered once daily while maintaining high penetration into pulmonary tissues and activity against

common bacterial pathogens that cause community acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI).[4-6] While the antibiotic space for CABP and ABSSSI continues to expand, OMC sets itself up as an alternative to patients who cannot take oral antibiotics such as FQs or β-lactams due to a good safety profile (low risk for *Clostridiodes difficile* infections) and minimal drug-drug interactions.

OMC's *in vitro* activity is vast, and its comparable MIC ranges to tigecycline for rapidly growing nontuberculous mycobacteria (NTM) have intrigued clinicians despite a lack of clinical data for this indication (table 1).[2,7,8,28] For the initial treatment of serious skin, soft tissue, and bone diseases caused by *M. abscessus,* the American Thoracic Society (ATS)/Infectious Diseases Society of America (IDSA) NTM diseases guidelines recommend a combination of a macrolide with amikacin and either high-dose cefoxitin or imipenem.[9] A recent ATS/IDSA clinical practice guideline on the treatment of NTM pulmonary disease recommends a combination of three agents, with the backbone of the initial and continuation phase including a macrolide.[10] Unfortunately, strains of NTM like *M. abscessus* demonstrate inducible macrolide resistance via an erythromycin resistance methylase (erm) gene. Resistance to macrolides and other guideline preferred therapies is common, leading to salvage management practices that can vary amongst providers. Preferred treatment options during the initial phase involve IV agent(s) in combination with oral agent(s), while the continuation phase involves use of oral/inhaled therapies. IV only options include imipenem, cefoxitin, tigecycline and amikacin (also available as inhaled product). In addition, while clinical data is limited, eravacycline and OMC have demonstrated similar *in vitro* activity to tigecycline against drug resistant *M. abscessus*. OMC's potential is notable due to a lack of oral options against *M. abscessus.* Current guideline recommended oral options are limited to azithromycin or clarithromycin, clofazimine, and linezolid or tedizolid, all of which carry notable tolerability and safety risks. Due to mycobacterial resistance and safety concerns of current treatment options, OMC's pharmacokinetic/pharmacodynamic properties have incited clinician use in *M. abscessus* infections.[2,7]

Chemistry and Mechanism of Action

OMC is a novel AMC which is a subclass of semisynthetic tetracycline antibiotics that are C-9-position derivatives of minocycline.[4,11] OMC specifically has an aminomethyl substituent at the C-9 position (9-dimethylpropylaminomethyl) and is associated with an increased spectrum of activity and decreased resistance relative to other tetracyclines.[12] Additionally, this C-9 group differentiates OMC from minocycline (without a C-9 substituent) and glycylcycline tetracyclines, such as tigecycline (9-*t*-butylglycylamido) and eravacycline (9-pyrrolidinoacetamido).[12,13]



The mechanism of OMC, is to chelate magnesium in the phosphate backbone of the RNA in the 30S subunit of the prokaryotic ribosome.[4,11] This results in nonfunctional ribosomes, and inhibition of protein synthesis and bacterial cell growth. Due to this mechanism of action, tetracyclines are clinically described as bacteriostatic. However, OMC has been observed to be bactericidal against certain organisms: streptococci, *Moraxella catarrhalis*, and *Haemophilus influenzae.*[12]

Microbiology

OMC demonstrates broad *in vitro* activity against Gram-positive and Gram-negative pathogens (see Table 1 & 2). Additional *in vitro* activity against comparators and isolates (including Anaerobes & Atypicals) collected from the 2016 SENTRY antimicrobial surveillance Program are demonstrated in Table 1&2.[11]

Table 1. *In Vitro* Activity of OMC and Comparators against Clinically Relevant Pathogens[11]

Species	Agent	MIC_{50} (mg/L)	MIC_{90} (mg/L)	MIC Ranges (ug/mL)	% S by CLSI [a]
Enterobacteriaceae[b]	TET	2	>16	≤0.25 to 16	64.2
	TGC	0.25	1	≤0.06 to 8	97.8
	OMC	1	8	0.12 to 32	NA
Staphylococcus aureus (MSSA)	TET	≤0.5	≤0.5	≤0.5 to 8	96.3
	TGC	0.06	0.12	≤0.015 to 0.25	100
	OMC	0.12	0.25	≤0.015 to 1	99.9
Staphylococcus aureus (MRSA)	TET	≤0.5	4	≤0.5 to 8	90.3
	TGC	0.06	0.12	≤0.015 to 0.12	100
	OMC	0.12	0.25	0.3 to 8	96.1
Enterococcus faecalis	TET	>16	>16	≤0.12 to 16	21.4
	TGC	0.06	0.12	≤0.015 to 0.12	100
	OMC	0.12	0.25	≤0.015 to 1	97.2
Enterococcus faecium	TET	>16	>16	≤0.12 to 16	42.6
	TGC	0.03	0.06	≤0.015 to 1	NA
	OMC	0.06	0.12	≤0.015 to 8	NA
Streptococcus pneumoniae	TET	≤0.25	>8	≤0.25 to 8	79.5
	TGC	0.03	0.06	0.015 to 0.25	99.4
	OMC	0.06	0.12	≤0.015 to 1	99.7
Streptococcus anginosus group	TET	0.5	>8	≤0.25 to 8	67.3
	TGC	0.03	0.03	≤0.008 to 0.12	100
	OMC	0.06	0.012	≤0.015 to 0.12	100
B-Hemolytic Streptoccucs[c]	TET	0.5	>8	≤0.25 to 8	54.7
	TGC	0.06	0.06	0.015 to 0.25	100
	OMC	0.06	0.12	0.03 to 0.5	NA
Haemophilus influenzae	TET	0.5	1	≤0.06 to 8	99.8
	TGC	0.12	0.25	0.06 to 1	96.1
	OMC	1	1	0.12 to 16	99.4
Clostriodioides difficile	TET	NA	NA	NA	NA
	TGC	0.25	0.25	0.25 to 4	NA
	OMC	0.25	0.5	0.25 to 8	NA
Bacteroides fragilis	TET	NA	NA	NA	NA
	TGC	0.5	2	0.5 to 8	NA
	OMC	0.5	4	0.25 to 16	NA

Abbreviations: MIC – minimum inhibitory concentration, %S – percent susceptible, CLSI – Clinical and Laboratory Standards Institute, TET– tetracycline, TGC – tigecycline, OMC – omadacycline; [a] based on Food and Drug administration breakpoints; [b]OMC is not active ; *in vitro* against *Morganella* spp., *Proteus* spp., *Providencia* spp.; [c]Includes *S. agalactiae, S. canis*, *S. dygalactiae*, and *S. pyogenes*

Table 2. *In Vitro* Activity of OMC and Doxycycline against Atypical Bacteria[8,11]

Species	Antimicrobial Agent	MIC50 (mg/L)	MIC 90 (mg/L)	MIC Ranges ug/mL	% S by CLSI
Mycoplasma pneumoniae	DCN TGC OMC	0.25 NA 0.12	0.5 NA 0.25	0.12 to 0.5 NA 0.12 to 0.25	NA NA NA
Legionella pneumophila	DOX TGC OMC	1 NA 0.25	1 NA 0.25	0.5 to 1 NA 0.06 to 1	NA NA NA
Chlamydia pneumoniae	DOX TGC OMC	0.125 NA 0.06	0.125 NA 0.25	0.06 to 0.25 NA 0.03 to 0.5	NA NA NA
Mycobacterium abscessus	DOX TGC OMC	1 1 1	2 2 2	0.06 to 8 0.06 to 8 0.06 to 8	NA NA NA
Mycobacterium chelonae	DOX TGC OMC	32 0.06 0.125	64 0.25 0.25	16 to 64 0.015 to 0.25 0.015 to 0.25	NA NA NA
Mycobacterium fortuitum	DOX TGC OMC	8 0.25 0.125	64 0.5 0.5	<0.06 to 64 0.015 to 1 0.03 to 1	NA NA NA

Abbreviations: MIC – minimum inhibitory concentration, %S – percent susceptible, CLSI – Clinical and Laboratory Standards Institute, DOX – doxycycline, TGC – tigecycline, OMC – omadacycline

Pharmacokinetics/Pharmacodynamics

OMC is available as an oral (PO) 150mg tablet and an intravenous (IV) 100mg vial. The bioavailability of the tablets is 34.5%, requiring a 300mg PO dose to achieve similar exposures to the 100mg IV dose. Antibacterial efficacy with tetracyclines is best correlated with the PK/PD parameter AUC/MIC ratio.[14] The AUC plasma exposure of the 300mg PO dose after a single dose and steady state is comparable to the 100mg IV dose (Table 3). [15,16] Exposure is considered linear and dose proportional.[3]

The oral tablets need to be administered on an empty stomach, avoiding dairy products, antacids or multivitamins by ≥ 4 hours.[15,16] Bioavailability was reduced 15-17% with a non-dairy meal 4 hours prior to dose, 40-42% with a non-dairy meal 2 hours prior to dose, and 59-63% with a dairy-containing meal 2 hours prior to dose.[17]

OMC has a lower volume of distribution compared to tigecycline (~7 L/kg) and eravacycline (4 L/kg), with an apparent steady-state volume of 190 L (~2.5 L/kg). Unlike other tetracyclines, OMC is poorly protein bound (20%), a feature that persists irrespective of rising plasma concentrations.[15-16] In a study of 58 healthy adults, higher steady state concentrations were achieved with OMC in the plasma, epithelial lung fluid (EFL), and alveolar concentrations (AC) than tigecycline (fig 1).[14]

OMC is a substrate of p-glycoprotein/ABCB1, however it does not undergo any noteworthy metabolism in humans. It is primarily excreted unchanged in the feces and urine (27%) with a half-life of ~16 hours for IV and 13-16 hours for oral, with no dose adjustments required for renal insufficiency (including ESRD on HD) or patients with hepatic impairment.[15]

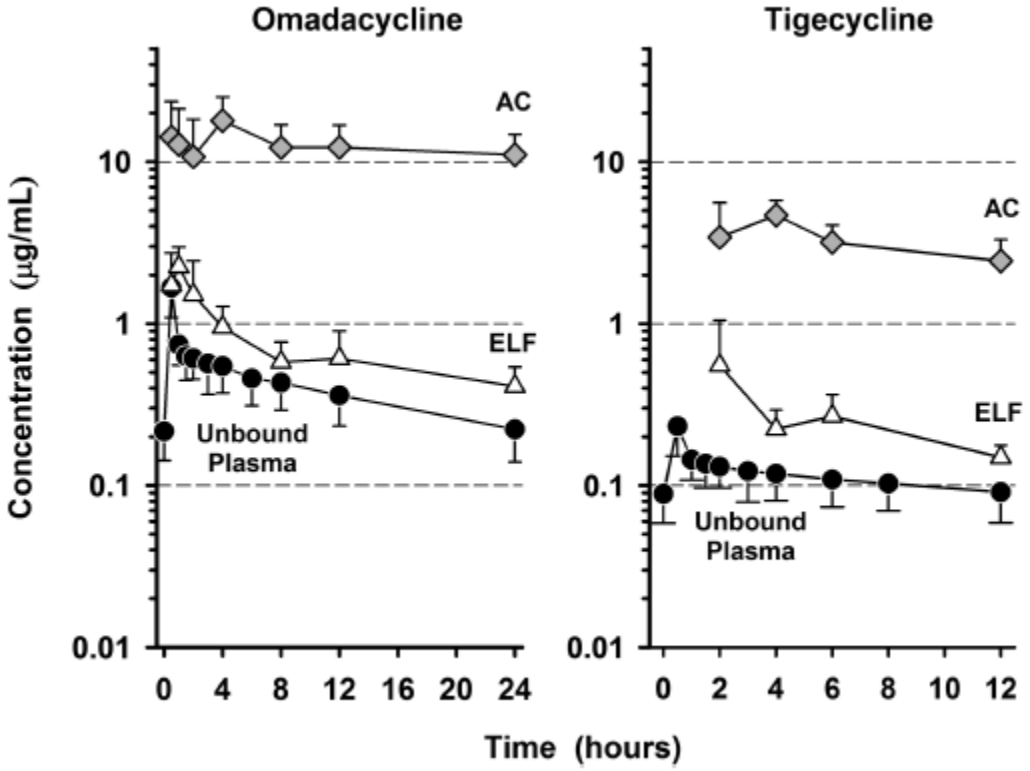


Fig 1. Mean plasma concentrations of OMC vs. tigecycline in plasma (closed circles), Epithelial Lung Fluid (EFL; open triangles), Alveolar Cells (AC; shaded diamonds).[14]

Resistance

Resistance to tetracycline agents may occur through a variety of mechanisms. The most common resistance mechanism is an energy-dependent efflux pump (*tet*K, *tet*L, or *tet*B), which decreases the concentration of antibiotic inside the bacterial cell.[4,11,13] Some bacteria have developed resistance via protective proteins (*tet*M, *tet*O, and *tet*S), which results in ribosomes that are less susceptible to chelation. A rare mechanism that is primarily associated with tigecycline, is the presence of oxidative enzymes that metabolize or inactivate the drug within the bacteria. While this rare resistance mechanism has not been demonstrated against OMC, it is still possible that OMC may be affected by it, as it has a similar structure to tigecycline.

However, *in vitro* data suggests that OMC retains activity against most tetracycline-resistant bacterial stains.[4,11,13] OMC has been observed to remain active in the presence of efflux pumps in Gram-positive organisms via *tet*K and in Gram-negative organisms via *tet*B. Resistance mechanisms found against OMC include a multidrug efflux pump (MexXY-OprM and MexAB-OprM) and tetracycline monooxygenase (TetX) which are not a widespread problem at this time. Additionally, low-level resistance due to mutations in the tetracycline binding site (16S rRNA) are still possible with OMC but are not overall concerning because this resistance mechanism results in a poor-functioning ribosome, decreasing the growth rate of the organism.[13]

Table 3. Pharmacokinetic (PK) parameters of OMC in Healthy Adult Subjects[15]

Dose and Route of Administration		100 mg IV	300 mg Oral	450 mg Oral
PK Parameters				
Cmax (ng/mL)	Single Dose	1507 (38.6)	548 (26.7)	874 (26.6)
	Steady State	2120 (32.0)	952 (44.2)	1077 (25.0)
AUC (h*ng/mL)	Single Dose	9358 (22.1)	9399 (27.2)	8977 (26.6)
	Steady State	12,140 (26.6)	11,156 (44.9)	13,367 (26.0)
Absorption				
Bioavailability	34.5%			
T_{max} Median in hours	Single Dose	0.55	2.5	2.5
	Steady State	0.5	2.5	2.5
Distribution				
Plasma Protein Binding	20%, not concentration dependent			
Volume of Distribution (L)	Single Dose	256	794	ND
	Steady State	190	ND	ND
Elimination				
Elimination Half-Life (hr)	Single Dose	16.2	14.96	13.45
	Steady State	16	15.5	16.83
Systemic Clearance	Single Dose	11.24	34.6	ND
	Steady State	8.8	ND	ND
Renal Clearance (L/hr)	2.4 to 3.3			
Metabolism	OMC is not metabolized			
Excretion (Mean % dose)	Urine	27 %	14.4 %	ND
	Feces	ND	81.1 %	ND

Adverse Effects

OMC has been compared to multiple other antibiotics for the treatment of CABP and ABSSSI with respect to efficacy and side effects. Adverse drug events (ADEs) were rarely significantly different to the comparator drugs (linezolid, FQs, nitrofurantoin, etc.) and each study had minimal dropouts due to these events. The most common ADEs associated with OMC were nausea (2-30%) and vomiting (3-17%), followed by headache (3-5%).[15,18,19] These effects were mild-to-moderate and transient for most patients in the study groups. However, gastrointestinal side effects (diarrhea, nausea, and vomiting) were more common (up to 20-30%) for patients on oral OMC. [19-21] In a phase-3 trial of OMC and linezolid (OASIS-1), nausea and vomiting were more common in the OMC group (12.4% vs 9.9% and 5.3% vs 5.0%, respectively).[25] In a study comparing oral OMC with oral linezolid (OASIS-2), the researchers found a significantly higher rate of nausea and vomiting with use of OMC, especially in patients taking oral doses of 450mg (32.6% vs 8.2%).[18] Similarly, in a phase-3 study of tigecycline and levofloxacin for treatment of CABP, tigecycline was also associated with increased rates of nausea

and vomiting (26.9% vs 8.5%, p<0.001 and 16.7% vs 6.6%, p=0.001, respectively), which were also described as being mild-to-moderate in most patients.[26] Additionally, in a phase-3 trial comparing eravacycline and ertapenem in the treatment of complicated intraabdominal infections (IGNITE-1), eravacycline was also associated with increased nausea compared to its competitor (8.1% vs 0.7%), however had similar results for vomiting.[27]

While gastrointestinal effects are the most common ADEs of OMC, others have also been described. In the OASIS-2 trial, researchers observed a higher rate of abnormal ALT levels compared to baseline in the OMC group compared to moxifloxacin (30% vs 20%)[18]. Some studies found potential cardiac risks with OMC, however a randomized trial found that there were no significant effects on cardiac conduction compared to placebo and moxifloxacin, but OMC was associated with an increase in heart rate.[22] Studies have not shown QTc prolongation to be associated with use of OMC. Additionally, infusion-site reactions were found at a slightly higher rate than that of linezolid (8% vs 6.2%).[21] Additionally, the package insert warns prescribers of potential risks of enamel hypoplasia and inhibited bone growth, which are relatively common in the tetracycline class.[15] Ultimately, OMC has been described as not having increased risks compared to the current standards of care for treatment of CABP and ABSSSI, and therefore is likely to be no more harmful in these populations.

Drug Interactions

Oral OMC, like other tetracycline derivatives, is associated with decreased bioavailability when taken with food, especially dairy. Drug-drug interactions are not as readily known for OMC, however it may be appropriate to use caution in agents that interact with other tetracycline derivatives. Agents that are associated with affecting absorption of tetracyclines include: mineral supplements, antacids, and bile acid sequestrants (among others).[15,17] Additional concerns with tetracycline agents is photosensitivity and bone loss, especially in pediatric patients; thus it is not recommended to use tetracyclines concomitantly with other medications that cause these effects.[15] *In vitro* studies have been performed, which suggest that OMC is not metabolized by and does not inhibit or induce CYP450 enzymes.[15] However, these studies do suggest that OMC is a substrate of P-glycoprotein (P-gp), which implies that drug interactions may occur with P-gp inhibitors, inducers, or other substrates including digoxin, calcium channel blockers (CCBs), and certain proton-pump inhibitors (PPIs).

Clinical Efficacy

Omadacycline for Community-Acquired Bacterial Pneumonia[23]

The OPTIC Trial is a Phase 3, double-blind, double-placebo, randomized non-inferiority trial comparing OMC with moxifloxacin in patients with CABP. The population included in this study were patients older than 18 years, with at least 3 symptoms of CABP (cough, purulent sputum, dyspnea, pleuritic chest pain), at least 2 abnormal vital signs, and at least 1 clinical sign or laboratory finding associated with CABP. Patients were excluded if they received another systemic antibiotic treatment within 72 hours, were diagnosed with hospital-acquired bacterial pneumonia, had empyema, had liver or renal insufficiency, or were immunocompromised. In this study, 774 patients went under randomization into two treatment groups: OMC (100mg IV Q12H on day 1 followed by 6-13 days 100mg IV Q24H) or moxifloxacin (400mg IV Q24H for 7-14 days) each with the option to transition to equivalent oral dosing after 3 days of IV treatment. The primary outcome of this trial was early clinical response at 72-120 hours, defined as survival with improvement of

symptom assessment on a 4-point scale (absent, mild, moderate, or severe) relative to baseline without worsening of other signs and symptoms and without receipt of rescue antibacterial therapy.
Analyses demonstrated that OMC is noninferior to moxifloxacin for the primary outcome (81.1% vs 82.7%, 95% confidence-interval (CI) -7.1-3.8 for intention-to-treat (ITT) group, and 86.5% vs 87.2%, 95% CI -5.7-4.3 for per-protocol group). Additionally, OMC was associated with lower rates of nausea (2.4% vs 5.4%), diarrhea (1.0% vs 8.0%), and *C. difficile* infection (0% vs 2.1%). A higher mortality rate was observed in the OMC group (2.1% vs 1.0%), which was not statistically significant. These deaths were in patients older than 65 years and causes of death varied (complications of infection, concomitant conditions, etc.), and the cause of this mortality imbalance was unable to be established.
This trial suggests that use of OMC in non-ICU patients with CABP may be an acceptable alternative to moxifloxacin. The safety of OMC was similar to that of other tetracyclines and was not considered treatment-limiting in most patients. The efficacy of OMC was non-inferior to moxifloxacin with respect to the primary endpoint (early clinical response). The primary strength of this study was that the researchers conducted and obtained extensive microbiologic testing. While pneumonia severity index (PSI) class III & IV were well represented, generalizability to the highest mortality risk group (PSI class V) is limited due their exclusions.

Table 4. Dosing for CABP and ABSSSI[15,18,23-25]

Indication	Trial	Day 1 (Loading dose)	Maintenance Dose
CABP	OPTIC	200mg IV over 60 mins x 1 OR 100mg IV over 30 mins every 12 hours for 2 doses	100mg IV over 30 mins daily OR 300mg PO daily
ABSSSI	OASIS-1	200mg IV over 60 mins x 1 OR 100mg IV over 30 mins every 12 hours for 2 doses	100mg IV over 30 mins daily OR 300mg PO daily
	OASIS-2	Day 1 and 2: 450mg PO daily	300mg PO daily

Abbreviations: CABP – community-acquired bacterial pneumonia, ABSSSI – acute bacterial skin and soft tissue infection, OPTIC – Phase 3 Trial Omadacycline for Community-Acquired Bacterial Pneumonia, OASIS-1 - Phase 3 Trial Omadacycline for Acute Bacterial Skin and Skin Structure Infections 1, OASIS-2 - Phase 3 Trial Omadacycline for Acute Bacterial Skin and Skin Structure Infections 2

Omadacycline for Acute Bacterial Skin and Skin Structure Infections[18,25]
OASIS-1 is a Phase 3, double-blind, randomized controlled trial comparing efficacy and safety of OMC and linezolid in treatment of acute bacterial skin and skin-structure infections (ABSSSIs).[25] 655 patients underwent randomization for treatment with either OMC (100mg IV Q12H x 1 day followed by Q24H x 6-13 days) or linezolid (600mg IV Q12H x 7-14 days) each with the option to transition to equivalent oral dosing after day 3. Patients included in this study were older than 18 years and diagnosed with a qualifying infection (wound infection from IV drug use or trauma, cellulitis, erysipelas, or major abscess), and the infection must have had a contiguous surface area of at least 75cm, exhibited evidence of erythema, edema, or induration, and had evidence of an inflammatory response. Patients were excluded if they received another antibiotic within 72

hours, infection was expected to require longer than 14 days for treatment, infection was associated with chronic lesions, ulcers, or wounds, if the patient had concomitant liver or renal insufficiency, or were immunocompromised. The primary endpoint of this study was early clinical response (reduction in lesion size of at least 20% at 42-72 hours after first dose of trial drug) in the modified ITT population (randomized patients with ABSSSIs with at least one Gram-positive pathogen).

OMC was noninferior to linezolid for early clinical response in the modified ITT (84.8% vs 85.5%, 95% CI -6.3-4.9). Patients with ABSSSIs with solely Gram-negative pathogen(s) were excluded from analysis, so information about efficacy of OMC in such skin infections is lacking. Results for all populations and subpopulations (infection types, lesion sizes, causative pathogens) were consistent with that of the primary endpoint (OMC is noninferior to linezolid).

OASIS-1 suggests that OMC may be a useful option for treatment of ABSSSIs caused by Gram-positive pathogen(s) or mixed Gram-positive and Gram-negative pathogens. Strengths of this study included high rates of causative pathogen identification in patients with common, large ABSSSIs. Limitations of this study include exclusion of common community-acquired skin infections (bite wounds, chronic infections, and diabetic skin ulcers) and infections with solely Gram-negative causative agent(s), and use of a study-mandated minimum therapy duration (unable to assess use for short-course (<7 days) or appropriate IV-to-PO transition).

OASIS-2 is another phase-3, double-blind, randomized controlled trial that sought to compare the efficacy and safety of oral OMC and oral linezolid therapy for patients with ABSSSI.[18] This trial had nearly identical inclusion and exclusion criteria to OASIS-1, however also excluded patients that were unable to tolerate oral medications. The difference between this trial and OASIS-1 is that patients exclusively received oral therapy, whereas patients received IV-only or were initiated on IV treatment and transitioned to PO in the OASIS-1 trial. In this study, 720 patients were randomized 1:1 for treatment with OMC (450mg PO Q24H x 2 days followed by 300mg PO Q24H x 5-12 days) or linezolid (600mg PO Q12H x 7-14 days). The primary endpoint of this study was early clinical response (reduction in lesion size of at least 20% at 43-72 hours after first dose of trial drug in the modified ITT population).

Oral OMC was noninferior to oral linezolid for the primary outcome (87.5% vs 82.5%, 95% CI -0.2-10.3). In this study, OMC was associated with higher rates of nausea and vomiting compared to linezolid (30% vs 8% and 17% vs 3%, respectively), especially during the loading phase with higher doses (OMC 450mg). There were no clinically relevant changes in vital signs or laboratory values, however OMC was associated with a higher rate of abnormal ALT levels compared to baseline (30% vs 20%).

OASIS-2 suggests that oral OMC may be appropriate for patients with ABSSSIs when prescribers want to treat these patients in the outpatient setting. As with OASIS-1, strengths of this study include enrollment of common, large ABSSSI infections and identification of a high proportion of causative pathogens. Limitations of this study included being underpowered for infection subtype analysis, exclusion of certain skin infections (as described above) and a study-mandated therapy duration.

OMC for NTM Disease

Clinical effectiveness of OMC in the treatment of NTM disease has been limited to case reports/series and

expert opinion.[2] In an *in vitro* study by Shoen et al, similar *in vitro* activities of OMC and tigecycline was demonstrated against rapidly growing NTMs *M. abscessus, M. chelonae*, and *M. fortuitum*.[8] A recent case series described clinical effectiveness for the treatment of *M. abscessus* in three of four patients. Clinical cure was demonstrated in one patient with cutaneous disease, one with pulmonary disease, and one with osteomyelitis and bacteremia. The fourth patient had cutaneous disease and was described as improving on ongoing treatment with clofazimine and azithromycin, but discontinued OMC due to nausea and vomiting. In each patient case, PO OMC was added to complete an all oral regimen.[7]

Conclusions

Three phase 3 clinical trials have established OMC as a safe and efficacious antibiotic for CABP and ABSSSI. While several antibiotic choices are available in both disease states, OMC can be considered as an alternative therapy choice where hypersensitivities, adverse effect profiles, or drug-drug interactions exist. In addition, OMC maintains stability against bacterial strains expressing the two most common tetracycline resistance mechanisms (efflux pumps and bacterial ribosomal protective proteins). Local antimicrobial susceptibilities should be followed if considering use as clinical efficacy in this setting is limited. Although off-label clinical effectiveness data in NTM infections has been encouraging, further collaboration among specialists reporting larger reports will convey if OMC develops a clinical niche in this space.

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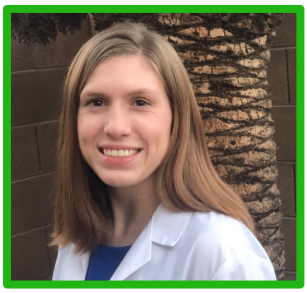

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The self-assessment quiz that can be found at the end of this article can be completed for 0.1 CEU of Continuing Pharmacy Education credit. The quiz may be completed online (http://madidtraining.org/newsletter/) at no cost for MAD-ID members. Non-members should print and mail the completed quiz, along with a $15.00 check made payable to MAD-ID to: MAD-ID, 537 Calico Retreat, Mt. Pleasant, SC 29464-2765. Your CE credit will be reported on CPE monitor within 4 weeks of receipt.

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Self-Assessment Questions

(To be completed online (http://mad-idtraining.org/newsletter/) or, in the case of non-MAD members, printed and mailed. You must achieve a grade of 80% of better to receive continuing education credit.)

1) Which of the following is true? (Learning objective #1)
    a. Like other tetracyclines, OMC is associated with high rates of resistance via efflux pump (*tet*K and *tet*L)
    b. It is recommended for a patient to avoid ingestion of divalent cations such as magnesium and calcium, because they may inactivate or affect absorption of oral OMC
    c. OMC has been shown to cover Gram-positive aerobes, but with minimal to no coverage of Gram-negative, atypical, and anaerobic pathogens
    d. Other than the modification of the C-9 position, OMC has an identical structure to tetracycline.

2) TC is a 65 yo man with a PMH of CAD and A-fib presenting with a polymicrobial wound infection. Among the following organisms speciated, OMC would be inactive against which organism? (Learning objective #1)
    a. *Enterococcus faecalis*
    b. *Streptococcus agalactiae*
    c. Methicillin-resistant *Staphylococcus aureus*
    d. *Proteus vulgaris*

3) Which of the following PK/PD characteristics best describes current OMC considerations in *M. abscessus* disease? (Learning objective #2)
    a. OMC's highly protein bound nature enhances free drug concentrations at the site of action
    b. OMC's once daily PO formulation as opposed to twice daily IV tigecycline
    c. 24-hour drug exposures of tigecycline are three-fold greater than OMC in alveolar cells
    d. OMC demonstrates more potent NTM in vitro activity than tigecycline

4) Which of the following patients is least likely to be experiencing an adverse reaction to OMC? (Learning objective #3)
    a. 47 yo female patient on treatment for a skin infection with significant nausea and vomiting on OMC 450mg PO Q24H
    b. 65 yo male patient on treatment for skin infection develops sunburn following a brief walk on a sunny day
    c. 24 yo developed a moderate and transient heart rate increase and QTc prolongation
    d. 72 yo female patient on treatment for ABSSSI with a headache after administration of her antibiotic

5) Which of the following patients would be eligible for use of a loading dose of OMC 450mg PO Q12H on the first day of therapy? (Learning objective #4)
    a. 32 yo female patient with cough, dyspnea, and purulent discharge
    b. 26 yo female patient with suspected cellulitis with erythema and inflammation
    c. 34 yo male patient with CXR positive for consolidation and positive sputum culture
    d. 42 yo male patient with a skin laceration due to major trauma currently on a ventilator without a feeding tube

Learning Activity Assessment

Please provide your honest assessment of the value of this learning activity so that we can continue to improve our offerings.

1. What is your profession
   - ☐ Pharmacist
   - ☐ Physician
   - ☐ Nurse
   - ☐ PA
   - ☐ Other

Please indicate your degree of agreement or disagreement with the following statements regarding this learning activity by indicating strongly agree (a), generally agree (b), no opinion (c), mildly disagree (d), or strongly disagree (e):

Criteria	Strongly agree (a)	Generally agree (b)	No Opinion (c)	Mildly disagree (d)	Strongly disagree (e)
2. The speaker(s) / author(s) adequately addressed the learning objectives	a	b	c	d	e
3. The speaker(s) / author(s) used an effective learning method	a	b	c	d	e
4. The content of the activity was relevant to my practice	a	b	c	d	e
5. This activity was free of commercial bias	a	b	c	d	e
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