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Discovery, pharmacology, and clinical profile of omadacycline, a novel aminomethylcycline antibiotic

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ABSTRACT

Omadacycline is novel, aminomethyl tetracycline antibiotic being developed for oral and intravenous (IV) administration for the treatment of community-acquired bacterial infections. Omadacycline is characterized by an aminomethyl substituent at the C9 position of the core 6-member ring. Modifications at this position result in an improved spectrum of antimicrobial activity by overcoming resistance known to affect older generation tetracyclines via ribosomal protection proteins and efflux pump mechanisms. In vitro, omadacycline has activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical pathogens including *Legionella* and *Chlamydia* spp. Omadacycline offers once daily oral and IV dosing and a clinical tolerability and safety profile that compares favorably with contemporary antibiotics used across serious community-acquired infections where resistance has rendered many less effective. In studies in patients with complicated skin and skin structure infections, including those with MRSA infections, omadacycline exhibited an efficacy and tolerability profile that was comparable to linezolid. Ongoing and planned clinical studies are evaluating omadacycline as monotherapy for treating serious community-acquired bacterial infections including Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP). This review provides an overview of the discovery, microbiology, nonclinical data, and available clinical safety and efficacy data for omadacycline, with reference to other contemporary tetracycline-derived antibiotics.
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1. Introduction

Omadacycline is a novel aminomethylcycline antibiotic being developed for once daily oral and intravenous (IV) administration for the treatment of community-acquired bacterial infections.[1] Omadacycline is being developed because of an increasing incidence of resistance to earlier tetracyclines including doxycycline and minocycline and the resistance faced by other classes of antibiotics.[2] Omadacycline differs from earlier generation tetracyclines because it overcomes the two primary tetracycline resistance mechanisms of ribosomal protection and efflux,[3] thus restoring the historical broad-spectrum efficacy of earlier generation tetracyclines.

Extensive results from in vitro studies have demonstrated antibacterial activity against Gram-positive and Gram-negative aerobes, anaerobes, and atypical pathogens including *Legionella* and *Chlamydia* spp.[4] Based on this profile, omadacycline was advanced into phase 2 and 3 studies for complicated skin and skin structure infections (cSSSI) where it showed efficacy and tolerability comparable to linezolid.[5,6] Omadacycline is currently undergoing development in phase 3 clinical studies for Acute Bacterial Skin and Skin Structure Infections (ABSSSI) and Community-Acquired Bacterial Pneumonia (CABP).

2. Discovery of omadacycline

2.1. Structure–activity relationship

Omadacycline is a stable, well-characterized crystalline drug substance that differs from other tetracyclines because of a novel modification at the C9 position.[1] Omadacycline is an aminomethylcycline antibiotic that is characterized by an aminomethyl group at the C9 position on the tetracycline structure.[1] Modifications at the C9 position result in improved antimicrobial potency for these new generation tetracyclines attributed to stability to ribosomal protection proteins and efflux pump mechanisms.[7,8]

A series of aminomethylcyclines with potent in vitro activity (minimum inhibitory concentration [MIC] $\leqslant$ 0.06–2.0 mcg/mL) were evaluated in vitro against Gram-positive bacteria possessing different tetracycline resistance mechanisms of ribosomal protection (Tet (M)) in *Staphylococcus aureus*, *Enterococcus faecalis*, and

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Streptococcus pneumoniae and efflux (Tet (K) in *S. aureus* and Tet (L) in *E. faecalis*).[1] Omadacycline was identified as one of the lead aminomethylcyclines in that series by classical structure–activity relationship determinations, which now represent a novel class of tetracycline-derived antibiotics with potent in vitro activity against tetracycline-resistant Gram-positive bacteria, including methicillin-resistant *S. aureus* (MRSA), and vancomycin-resistant enterococci (VRE).

Omadacycline differs from the glycylcycline tetracyclines, tigecycline (9-*t*-butylglycylamido) and eravacycline (TP-434, 7-fluoro-9-pyrrolidinoacetamido-6-demethyl-6-deoxytetracycline) by the presence of an aminomethyl group at the C9 position (Fig. 1).[9,10] Modifications at the C9 position result in improved antimicrobial potency for these new generation tetracyclines attributed to stability to ribosomal protection proteins and efflux pump mechanisms.[7,8] Omadacycline has other absorption, distribution, metabolism, and excretion (ADME) attributes that further distinguish it from the glycylcycline class of tetracyclines. These differences will be discussed further below under Pharmacology.

2.2. Omadacycline mechanism of action

In vitro macromolecular synthesis assays with radiolabeled substrates demonstrated that omadacycline inhibits protein synthesis while having no significant effect on RNA, DNA and peptidoglycan synthesis. Further, omadacycline binds to the tetracycline binding site on the 30S subunit of the bacterial ribosome[3,11] with enhanced binding similar to tigecycline based on additional molecular interactions.[12]

2.3. Overcoming tetracycline resistance

There are two basic and clinically important mechanisms of tetracycline resistance: tetracycline efflux[2] and ribosome protection.[2] Tetracycline efflux proteins are membrane-associated proteins that recognize and export tetracycline from the cell, thus reducing the intracellular drug concentration. They are found in both Gram-positive and Gram-negative bacteria. Ribosomal protection proteins are cytoplasmic proteins that bind the ribosome, causing an alteration in ribosomal conformation that prevents tetracycline from binding.[13]

The majority of efflux proteins result in bacterial resistance to tetracyclines but not to minocycline, aminomethylcyclines or glycylcyclines.[2,3] However, the Gram-negative *tet*(B) gene produces an efflux protein, which produces bacterial resistance to both tetracycline and minocycline but not aminomethylcyclines and glycylcyclines.[2,3] Ribosomal protection proteins produce broad resistance to tetracyclines that exceeds that observed with bacteria that carry efflux proteins that impact doxycycline and minocycline.[2] Of the 10 or more ribosomal protection proteins, the Tet (M) and Tet(O) proteins have been most closely characterized and both omadacycline and tigecycline retain activity against both types.[2,3]

The in vitro activity of omadacycline and other aminomethylcyclines was tested against Gram-positive bacteria that possessed the primary tetracycline resistance mechanisms of ribosomal protection and efflux.[3,14] Omadacycline exhibited excellent activity against clinical bacterial isolates possessing a variety of tetracycline resistance mechanisms. Furthermore, the ability of omadacycline to inhibit whole-cell protein synthesis was not affected in whole-cell assays by the presence of either tetracycline efflux (Tet(K)) or ribosome protection (Tet(O)).[3,14] Omadacycline also demonstrates potent in vitro activity against TET-resistant Gram-positive bacteria that were resistant to other antibiotics including quinolones and glycopeptides as well as tetracyclines.[15]

The ability to select resistance in vitro is often used to indicate the potential for bacteria to become resistant to an antibiotic either during therapy (often as a single mutational event) or over the lifetime of the antibiotic (often due to a series of mutations). Bacteria that carry any of the classic tetracycline resistance genes conferring either ribosomal protection or a tetracycline efflux pump have remained susceptible to omadacycline. No Gram-positive clinical isolates with reduced susceptibility to omadacycline (MIC $\geqslant$ 4 mcg/mL) have been identified including strains that are resistant to currently available antibiotics, such as methicillin, vancomycin, and doxycycline.[4,16] Selection of single-step resistant mutants in *S. aureus* strains, including those carrying tetracycline resistance determinants *tet*(M) and *tet*(K), was not observed with omadacycline. Further, in multiple step passage studies conducted over 10 days, no selection for multi-step resistant mutants in tetracycline sensitive and tetracycline-resistant strains of *S. aureus* was observed with omadacycline.[3,14] Compared to MICs in susceptible strains (MIC range: $\leqslant$0.06–0.5 mcg/mL), MICs were not significantly affected by the presence of Tet(M) (MIC range: 0.125–0.5 mcg/mL) or Tet(L) or Tet(K) (MIC range: 0.125–0.25 mcg/mL) in resistant strains. Therefore, target-based resistance to omadacycline or resistance based on mutational changes to tetracycline efflux or ribosome protection are unlikely to arise quickly.

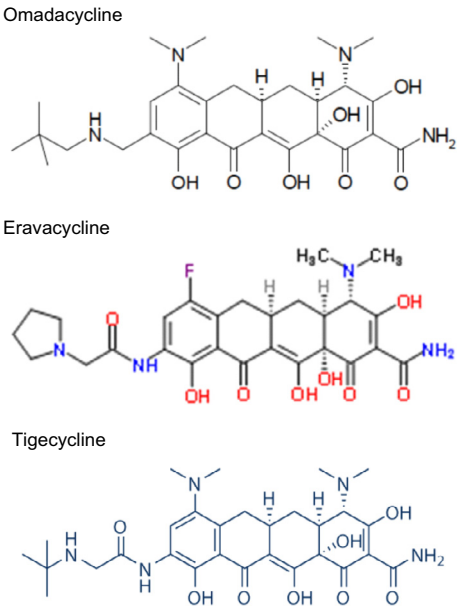

Figure 1. Chemical structures of new generation tetracyclines, omadacycline, eravacycline, and tigecycline.[3,9,10]

3. In vitro microbiology

The in vitro activity of omadacycline has been evaluated in numerous studies against a broad range of Gram-positive and Gram-negative aerobic bacteria as well as many anaerobes and atypical pathogens.[4,16–19] In particular, in vitro activity has been demonstrated against tetracycline-resistant pathogens including MRSA, PRSP, and VRE.[4,16]

3.1. Gram-positive bacteria

Gram-positive pathogens including drug-resistant strains are highly sensitive in vitro to omadacycline (data on file).[16,19–22] A comparison of in vitro activity for various antibiotics against *S. aureus* found that the MIC_{90} for all isolates collected during

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