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OMADACYCLINE: A NOVEL TETRACYCLINE ANTIBIOTIC IN THE TREATMENT OF CELLULITIS

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ABSTRACT:

Cellulitis is a common acute bacterial infection involving the skin and subcutaneous tissues and is a major component of acute bacterial skin and skin structure infections (ABSSSI). The increasing prevalence of antibiotic-resistant organisms, particularly methicillin-resistant *Staphylococcus aureus* (MRSA), has complicated its management. Omadacycline, a novel aminomethylcycline antibiotic, has been developed to overcome resistance mechanisms associated with traditional tetracyclines. It exhibits broad-spectrum activity against Gram-positive, Gram-negative, and atypical pathogens. Clinical trials have demonstrated its efficacy and safety in the treatment of ABSSSI, including cellulitis. This review provides a comprehensive overview of the pharmacological profile, mechanism of action, antimicrobial spectrum, clinical efficacy, and safety of omadacycline in the management of cellulitis.

KEYWORDS: Acute bacterial skin and skin structure infections, Omadacycline, Cellulitis, Tetracycline, Linezolid.

INTRODUCTION

Cellulitis is a common acute bacterial infection of the skin and subcutaneous tissues, most frequently affecting the lower extremities. It is primarily caused by Gram-positive organisms such as *Streptococcus* species and *Staphylococcus aureus*. Clinically, it presents with redness, swelling, warmth, pain, and sometimes systemic symptoms such as fever.

Despite the availability of various antibiotic therapies, the management of cellulitis remains challenging due to the increasing prevalence of antibiotic-resistant pathogens, particularly

methicillin-resistant *Staphylococcus aureus* (MRSA). Additionally, limitations in current treatment options, including adverse effects and reduced efficacy, highlight the need for newer, effective antimicrobial agents.

Omadacycline, a novel aminomethylcycline antibiotic, has emerged as a promising therapeutic option for the treatment of acute bacterial skin and skin structure infections (ABSSSI), including cellulitis. It is designed to overcome common tetracycline resistance mechanisms and exhibits broad-spectrum activity against both Gram-positive and Gram-negative organisms.

This review aims to provide a comprehensive overview of the pharmacological profile, mechanism of action, clinical efficacy, and safety of omadacycline in the treatment of cellulitis.

MATERIALS AND METHODS:

The efficacy and safety of omadacycline in acute bacterial skin and skin structure infections (ABSSSI), including cellulitis, were evaluated using integrated data from two Phase III clinical trials: OASIS-1 (global) (NCT02378480)and OASIS-2 (US-only)(NCT02877927).

Both were multicenter, randomized, double-blind, double-dummy, noninferiority studies comparing omadacycline with linezolid in adult patients meeting FDA-defined ABSSSI criteria.

Table no:1 Dosing of omadacycline.

CHARACTERISTIC	OASIS-1	OASIS-2
Traeatment duration	7-14 days	7-14 days
Omadacycline dosing	100mg IV q12h for 2 doses, then 100mg IV q24h for 2days Optional at >3 days: transition to 300mg PO q24h	450mg PO q24j for 2 doses, then 300mg PO q24h
Linezolid dosing	600mg IV q12h Optional at >3days: transition to 600mg PO q12h	600mg PO q12h
FDA primary endpoint	ECR at 48-72h	ECR at 48-72h
EMA primary endpoint	Investigator-assessed clinical response at PTE	Investigator-assessed clinical response at PTE
Prior antibiotics prohibited	Within 72 h of randomization, any other systemic or topical antibiotic agent potentially effective for ABSSSI	Within 72 h of randomization, any other systemic or topical antibiotic agent potentially effective for ABSSSI
Concomitant antibiotics prohibited	Any other systemic antibiotic against known/suspected ABSSSI pathogens, except in	Any other systemic antibiotic agent potentially effective for ABSSSI, except in cases of

	cases of clinical failure Any topical antibacterial agent active against known/suspected ABSSSI pathogen on study infection	clinical failure Any topical antibacterial agent active against known/ suspected ABSSSI pathogen on study infection

In OASIS-1, patients received intravenous (IV) omadacycline or linezolid with an option to switch to oral therapy after day 3 upon clinical improvement. OASIS-2 evaluated oral-only formulations of both drugs. The primary analysis population was the modified intent-to-treat (mITT) group, excluding patients with baseline gram-negative–only infections. Additional populations included clinically evaluable (CE), microbiological mITT (micro-mITT), and safety populations.

The primary endpoint for the FDA was early clinical response (ECR) at 48–72 hours, defined as ≥20% reduction in lesion size, survival, and no need for rescue antibiotics. The European Medicines Agency (EMA) coprimary endpoint was investigator-assessed clinical response (IACR) at posttreatment evaluation (7–14 days after last dose), defined as resolution of infection without further antibiotic therapy.

Microbiological outcomes were assessed at end of treatment and posttreatment using culture-based methods. Safety evaluations included monitoring adverse events, vital signs, laboratory parameters, and electrocardiograms.

Noninferiority was assessed using a 10% margin, with two-sided 95% confidence intervals calculated via the Miettinen–Nurminen method. Omadacycline was considered noninferior if the lower bound of the confidence interval exceeded –10%.

RESULT AND DISCUSSION:

1. OMADACYCLINE:

1.1` US Food and Drug administration [FDA] approval

Omadacycline is an aminomethylcycline antibiotic belonging to the tetracycline class. It stops the bacterial ribosomal subunit 30S from working. Unlike other tetracycline antibiotics, omadacycline has structural alterations at the C9 and C7 positions of the core tetracycline rings, which enable ribosomal defence mechanisms and stability in the efflux pump associated with tetracycline antibiotic resistance.The FDA approved omadacycline in October 2018 for the treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSI). This drug has not yet received approval from the European Medicines Agency.

Both oral and intravenous forms are given once a day. The medication enables medical providers to treat patients intravenously (IV) before switching them to oral therapy. The FDA defines an acute bacterial skin and skin structure infection (ABSSSI) as cellulitis/erysipelas, a wound infection, or a significant cutaneous abscess with an area of erythema, induration, or fluctuance of 75 cm for the purposes of clinical trial evaluations of antimicrobial medications in skin and soft tissue infections.

2. MODE OF ACTION & MICROBIAL ACTIVITY:

Like any other tetracycline binding site, omadacycline functions by binding at the microbial 30s ribosomal subunit with exceptionally high specificity and by inhibiting the synthesis of bacterial DNA, RNA, and peptidoglycan. Following this connection, bacterial protein synthesis is hampered by the inability to incorporate amino acids into peptides, which results in either cell death or stasis.

This medication was created as an updated version of earlier tetracyclines to prevent resistance, which restricts their usage in infections, and to eliminate additional adverse effects associated with glycylcycline tetracycline. Depending on the kind of organism, omadacycline can have either a bactericidal or bacteriostatic effect.In vitro bactericidal activity was shown against streptococci, M. catarrhalis, and H. influenzae, whereas bacteriostatic activity was found against enterococci, S. aureus, and E. coli in a study involving 85 strains of various bacteria.

Omadacycline has a wide range of activity against atypical bacteria like Chlamydia and Legionella as well as aerobic and anaerobic Gram positive and Gram negative microorganisms. Additionally, it is effective against drug-resistant bacteria such as vancomycin-resistant Enterococcus, penicillin-resistant and multidrug-resistant Streptococcus pneumoniae, and methicillin-resistant Staphylococcus aureus (MRSA).

3. RESISTANCE:

Tetracycline resistance is thought to arise from organisms that encode specific genes, such as tet(A), tet(B), tet(K), and tet(L), which mediate the efflux mechanism, and tet(O), tet(S), and tet(M), which are also involved in ribosomal protection. Drug breakdown and mutations at rRNA locations may also lead to tetracycline resistance.For example, even when tetracycline becomes numb in the presence of the ribosomal protective protein Tet(O), omadacycline still inhibits the formation of the protein. Tetracycline efflux is caused by the gene tet(K), although this gene has no effect on omadacycline.

4. PHARMACODYNAMICS

4.1 Cardiovascular Electrophysiology:

Nonclinical and clinical evidence, including electrocardiogram analysis in the phase 3 clinical investigations, which included moxifloxacin as a control group, showed no clinically significant QTc prolongation at the maximum recommended dose of omadacycline.

4.2 Increase in Heart Rate: Cardiac Physiology:

In phase 1 trials conducted on healthy volunteers, omadacycline therapy in both single and repeated dosages has been linked to transient, dose-dependent increases in heart rate. There are no known therapeutic ramifications to this discovery.

In a typical radiolabeled ligand binding experiment, omadacycline was demonstrated to prevent scopolamine from binding to the M2 subtype of the muscarinic acetylcholine receptor. The heart has muscarnic M2 receptors, which are mediators of parasympathetic input. In response to receptor activation, the potassium conductance of the acetylcholine-dependent channel membrane increases, delaying depolarization and lowering pacemaker activity in the sinoatrial node.

5. PHARMACOKINETICS

5.1 ABSORPTION:

Omadacycline has a mean Tmax of 2.5 hours and a mean absolute oral bioavailability of 34.5% when taken orally. With many dosages, omadacycline shows a 1.5 accumulation factor. The official labeling states that food does not significantly affect the rate or extent of absorption, although there is conflicting evidence that suggests food may reduce the bioavailability of omadacycline taken after eating. Omadacycline appears to significantly infiltrate the lungs, as evidenced by exposure in epithelial lining fluid and alveolar cells, which are, respectively, 25.8 and 1.5 times greater than plasma exposure following IV dosing.

5.2 VOLUME OF DISTRIBUTION:

After a single 100-mg IV dose, the Vd was 256 L (CV, 25.6%). The steady-state volume of distribution (Vd) of omadacycline after 10 mg IV doses was 190 L (CV 27.7%) [21]. On the other hand, following a single 300 mg oral administration, the volume of distribution (Vd) of omadacycline was 256 L (variation coefficient, 23.6%).

5.3 PROTEIN BINDING:

Omdacycline has non-linear protein binding, maintaining a 20% binding rate at all concentrations.

5.4 METABOLISM:

There is no proof that omadacycline can be metabolized by humans. Omadacycline is not metabolized, according to in vitro studies using human liver microsomes and hepatocytes.

5.5 ROUTE OF ELIMINATION:

In 27% of instances, the kidneys eliminated omadacycline following intravenous therapy. It was discovered that 81.1% of the oral dosage was eliminated in the feces and 14.4% was eliminated via the kidneys. Neither renal nor hepatic impairment appear to have a clinically meaningful effect on elimination.

6. PHASE 3 CLINICAL TRIALS OF OMADACYCLINE:

The first Phase 3 clinical trial, OASIS 1, was carried out by Paratek Pharmaceuticals to test the safety and efficacy of omadacycline versus linezolid in the treatment of acute bacterial skin and skin structure infections. From June 2015 to August 2016, 78 locations worldwide participated in this interventional, randomized, double-blind, non-inferiority trial. For the purpose of the study, participants were split into two groups at random. Before transitioning to a 300 mg oral dose, the first group was given two 100 mg intravenous doses of omadacycline spanning a minimum of three days.

Before moving to a 600 mg oral dosage, the second group got six intravenous doses of 600 mg of linezolid.A 20% reduction in the size of the lesion was noted in the first phase of the therapy, known as an early clinical response (ECR), 48 to 72 hours after the first dose. The second phase of the treatment was known as a post-therapeutic evaluation (PTE), which recorded the clinical efficacy of the treatment based on the patient's alive status and improvement in symptoms 0 to 37 days after the treatment was finished.

Table no:2 Clinical trials of omadacycline.

SPONSOR	**Paratek Pharmaceuticals**	**Paratek Pharmaceuticals**
TRIAL SITE	Global Multi-centre – 78 sites	US Only Multi Centre
SAMPLE SIZE	655	735
TRIAL DURATION	June 2015-Aug 2016	Aug 2016- May 2017
TRIAL TYPE	Interventional, Randomized, Double	Interventional, Randomized, Double

		blind, non-inferiority		blind, non-inferiority	
TRIAL INDICATION		ABSSSI		ABSSSI	
TRIAL PROCEDURE	Omadacycline	2 doses IV 100mg every 24 hours for the minimum of 3 days & switched to 300 mg Oral		2 doses of 450 mg Oral drug Once daily then continued with 300 mg oral dose once daily	
	Linezolid	6 Doses IV 600mg q12 hourly for the minimum of 3 days & switched to 600 mg Oral		600 mg Oral dose twice daily	
THERAPY DURATION		7 – 14 days		7 - 14 days	
CLINICAL OUTCOMES	Early clinical response	Omadacycline	84.8%	Omadacycline	87.5%
		Linezolid	85.5%	Linezolid	82.5%
	Post therapeutic evaluation	Omadacycline	86.1%	Omadacycline	84%
		Linezolid	83.6%	Linezolid	81%
	Adverse events(Gastro intestinal events – nausea, vomiting and diarrhoea)	Omadacycline	48.3%	Omadacycline (mild to moderate nausea and vomitting)	30 % & 17 %
		Linezolid	45.7%	Linezolid (Mild to moderate nausea and vomitting)	8% & 3 %

The Phase 3 clinical trial OASIS II, which compared the safety and effectiveness of oral omadacycline versus linezolid in acute bacterial skin and skin structure infections, was also funded by the same pharmaceutical business. After being divided into two groups at random, the first group was given two doses of 450 mg of omadacycline tablets, followed by 300 mg once daily, while the second group was given 600 mg of linezolid tablets twice daily. The drug was given for seven to fourteen days, depending on how severe the condition was. The data were statistically analyzed in reference to the previous trial.

CONCLUSION:

Cellulitis remains a significant clinical concern due to its high prevalence and the increasing incidence of antibiotic-resistant pathogens, particularly methicillin-resistant *Staphylococcus aureus* (MRSA). The limitations of conventional antibiotic therapies highlight the need for newer and more effective treatment options.

Omadacycline, a novel aminomethylcycline antibiotic, offers a promising alternative due to its ability to overcome common tetracycline resistance mechanisms and its broad-spectrum antimicrobial activity against Gram-positive, Gram-negative, and atypical organisms. Clinical evidence from Phase 3 trials has demonstrated that omadacycline is both effective and well tolerated, with efficacy comparable to established agents such as linezolid.

Additionally, the availability of both oral and intravenous formulations provides flexibility in clinical management, facilitating early hospital discharge and improved patient compliance. Overall, omadacycline represents a valuable addition to the therapeutic options for cellulitis and other acute bacterial skin and skin structure infections. However, further studies are recommended to evaluate its long-term safety and effectiveness in broader patient populations.

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