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### Treatment of wound infection using omadacycline versus linezolid: Pooled results from phase 3 randomized, double-blind, multicenter studies (OASIS-1 and -2)

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**Background:** Deployed military personnel are at risk for combat wound infections due to drug-resistant or multidrug-resistant organisms. New, effective antibiotic treatment strategies that are easy to administer in field hospital settings are needed to effectively counter the threat of antimicrobial resistance. Omadacycline (OMC) is a novel aminomethylcycline antibiotic approved in the USA for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSI) in adults. Modifications in the chemical structure of OMC allow it to overcome the two main mechanisms of tetracycline resistance: efflux pumps and ribosomal protection. OMC is available as an IV-to-oral or oral-only treatment option for ABSSSI, and demonstrated reliable *in vitro* and *in vivo* activity against a number of pathogens, including *Staphylococcus aureus* (methicillin-resistant [MRSA] and methicillin-susceptible [MSSA]), *Streptococcus pyogenes*, *Enterococcus faecalis* (vancomycin-susceptible [VSE] or vancomycin-resistant [VRE]), and *Klebsiella pneumoniae* and *Escherichia coli* (extended-spectrum β-lactamase negative or positive). Here we report pooled efficacy and safety results for patients with wound infection who were not people who inject drugs (PWID), from the IV-to-oral Omadacycline in Acute Skin and Skin Structure Infections (OASIS-1) study and the oral-only OASIS-2 study.

**Methods:** In OASIS-1 (NCT02378480) patients received IV OMC (Day 1: 100 mg q12h; Day 2+: 100 mg q24h) or linezolid (LZD; 600 mg q12h) with a possible transition to oral regimens after at least 3 days of IV therapy (OMC: 300 mg q24h; LZD: 600 mg q12h). Patients were eligible to transition to oral therapy if there was evidence of local and systemic improvement (temperature ≤100°F, return of white blood cell count and differential toward normal range, no increase in lesion area compared to baseline, and decrease in extent and intensity of ≥1 inflammatory finding). OASIS-2 (NCT02877927) investigated oral-only OMC (Day 1, 2: 450 mg q24h; Day 3+: 300 mg q24h) versus LZD (600 mg q12h). In both studies, eligible patients were ≥18 years of age and had qualifying ABSSSI with lesion size measuring ≥75cm$^2$ within 24 hours before randomization. Total duration of therapy for both studies was 7–14 days. Data analysis populations included modified intent-to-treat (mITT, comprising all randomized patients without a sole Gram-negative ABSSSI pathogen, as the comparator LZD does not provide Gram-negative pathogen coverage); and micro-mITT (all mITT patients who had ≥1 Gram-positive causative pathogen identified from the ABSSSI site or blood culture). As recommended by the Food and Drug Administration, the primary efficacy end point was early clinical response (ECR) in the mITT population. Early clinical response was determined programatically and defined as survival with a reduction in lesion size of at least 20% at 48–72 hours after the first dose without rescue antibacterial therapy. A key

secondary efficacy end point was survival with resolution or improvement in signs and symptoms of infection (to the extent that further antibacterial therapy was unnecessary) at the post-treatment evaluation (PTE; 7 to 14 days after the last dose) in the mITT population. Safety was assessed on the basis of adverse events, vital signs, electrocardiograms (ECGs), and laboratory results. A post-hoc subanalysis was performed on the pooled OASIS-1 and -2 data for patients with wound infection who were not PWID.

**Results:** In the pooled mITT population, 87 patients had wound infection, 37 of whom were treated with OMC and 50 with LZD. For OMC- and LZD-treated patients with wound infection, respectively, 67.6% and 48.0% were male, mean age was 47.3 years and 52.0 years, and mean body mass index was 28.9 $kg/m^2$ and 29.4 $kg/m^2$. From medical history, most patients (OMC: 78.4%, LZD: 66.0%) reported the study wound infection resulted from recent trauma and 18.9% and 6.0%, respectively, reported it resulted from a surgical procedure. In the micro-mITT population, 26 patients receiving OMC and 37 receiving LZD had wound infection, in whom Gram-positive organisms (aerobes) were the predominant pathogens (96.2%, 100.0%). Respectively, 61.5% and 70.3% of patients had *S. aureus*, 23.1% and 32.4% had MRSA, 38.5% and 37.8% had MSSA, 7.7% and 27.0% had *S. pyogenes*, and 19.2% and 13.5% had VSE. Early clinical response in the mITT population in patients with a wound infection was achieved in 34 (91.9%) patients receiving OMC and 41 (82.0%) patients receiving LZD (difference 9.9; 95% CI, −5.6, 24.3). Success at post-therapy evaluation (PTE; 7–14 days after last dose) in the mITT population was comparable between OMC and LZD (n=34, 91.9% vs n=39, 78.0%; difference 13.9%; 95% CI, −2.1, 28.8). Success at PTE in the micro-mITT population with wound infection was also comparable between OMC and LZD for mono-microbial Gram-positive infection (n=26, 92.9% vs n=37, 76.9%; difference 15.9%; 95% CI, −11.1, 37.1), polymicrobial Gram-positive infection (n=5, 80.0% vs n=5, 60.0%; difference 20.0%; 95% CI, −38.0, 67.0), and polymicrobial mixed (Gram-positive and -negative) infection (n=7, 100.0% vs n=4, 66.7%; difference 33.3%; 95% CI, −11.1, 71.1). When analyzed by baseline pathogen, clinical success at PTE for OMC- and LZD-treated patients, respectively, was observed in 15 (93.8%) and 19 (73.1%) patients with *S. aureus*, 6 (100.0%) and 9 (75.0%) with MRSA, 9 (90.0%) and 10 (71.4%) with MSSA, 1 (50.0%) and 7 (70.0%) *S. pyogenes*, and 5 (100.0%) and 3 (60.0%) with VSE (micro-mITT population). The number of patients with wound infections from the safety population (OMC, n=40; LZD, n=51) with at least one treatment-emergent adverse event (TEAE) was 16 (40.0%) and 18 (35.3%) in OMC and LZD, respectively. Nausea was the most frequent TEAE, reported in 8 (20.0%) patients receiving OMC and 3 (5.9%) patients receiving LZD. Serious TEAEs were observed in 1 (2.5%) and 2 (3.9%) of patients receiving OMC and LZD, respectively.

**Conclusions:** In adults with wound infection who were not PWID, OMC was an effective treatment. OMC had clinical efficacy for the most frequently isolated bacterial pathogens, including *S. aureus* and notably MRSA. Given the reliable *in vitro* and *in vivo* activity of OMC against a number of pathogens, its ability to overcome the most common resistance mechanisms to tetracyclines, and its flexible administration options, OMC may offer a unique treatment option to address combat wound infections, including those due to drug-resistant organisms.

**LEARNING OBJECTIVES**

- Recognize the novel aminomethylcycline, omadacycline, as an approved oral and intravenous tetracycline-class antibiotic (USA) for the treatment of adults with acute bacterial skin and skin structure infection.
- Describe the efficacy of omadacycline for the treatment of acute bacterial skin and skin structure infection resulting from wound infections, with particular emphasis on frequently isolated bacterial pathogens, including *Staphylococcus aureus* and methicillin-resistant *Staphylococcus aureus* (MRSA).
- Discuss the relevance of omadacycline as a novel approach to meet the unique medical needs of the warfighter and counter the threat of antibiotic resistance, offering iv-to-oral and oral only treatment options