Subinhibitory concentrations of omadacycline inhibit Staphylococcus aureus hemolytic activity in vitro

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Background

Virulence factor production contributes to the ability of a microorganism to cause an infection, as well as the severity of the infection.^{1–3} Virulence factors can cause tissue destruction by interfering with the host response to infection or causing uncontrolled inflammation.

Favorable treatment outcomes can be achieved by killing the infecting organism or preventing its multiplication. Agents that can also prevent or inhibit virulence factor production and/or activity may offer additional benefit.

In animal models of Staphylococcus aureus infection, α-hemolysin, a pore-forming exotoxin that can damage the host cell's plasma membrane, has been shown to be a key virulence factor.^{1–5}

Most, if not all, virulence factor production depends on protein synthesis, and exposure to protein synthesis inhibitors at levels at or below those that inhibit bacterial multiplication can decrease α-hemolysin expression.^{6–10} Therefore, at the recommended treatment dosing for protein synthesis inhibitors, it may be possible to achieve exposure to treat infections caused by S. aureus based on inhibition of multiplication, as well as inhibition of production of S. aureusassociated virulence factors.

Omadacycline, a novel aminomethylcycline antibiotic in the tetracycline class of bacterial protein biosynthesis inhibitors, shows activity against methicillin-sensitive and methicillin-resistant S. aureus, and is approved in the United States for treatment of community-acquired bacterial pneumonia (CABP) and acute bacterial skin and skin structure infections (ABSSSI) in adults.¹¹

Methods

All experiments used the methicillin-sensitive S. aureus strain Wood 46 (ATCC 10832), a laboratory strain known to secrete high levels of α -hemolysin.

Minimum inhibitory concentrations (MICs) of omadacycline and comparator antibiotics were determined. Comparators included other protein synthesis inhibitors (tetracycline, clindamycin, linezolid) and cell wall inhibitors (vancomycin, cephalothin).

Growth of S. aureus with all antibiotics was determined and the percentage of hemolysis assayed. "Washout" experiments were performed with omadacycline only.

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Suppression of virulence factors may contribute to the clinical efficacy of omadacycline

Objective

To determine the durability of inhibition and effect of sub-growth inhibitory concentrations of omadacycline on Staphylococcus aureus hemolytic activity.

Conclusions

Omadacycline inhibited S. aureus hemolytic activity in vitro at subgrowth inhibitory concentrations and inhibition was maintained for ≥ 4 hours after removal of extracellular drug.

The suppression of virulence factors, in addition to the *in vitro* potency of omadacycline, may contribute to the efficacy of omadacycline for ABSSSI and CABP due to virulent strains of *S. aureus*.

This finding could apply to other organisms and other virulence factors that require new protein synthesis to establish disease.



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Results

S. aureus cultures treated with 1/2 or 1/4 the MIC of omadacycline for 4 hours showed hemolysis units/10⁸ CFU of 47% and 59% of vehicle-treated cultures, respectively (Figures 1A and 1B).

In washout experiments, exposure to as little as 1/4 the MIC of omadacycline for 1 hour decreased the hemolysis units/10⁸ CFU by 60% for 4 hours following removal of the drug (**Figure 2**).

Figure 1: Hemolytic activity of S. aureus Wood 46 after 4 hours' growth with (A) 1/2 and (B) 1/4 the MIC of omadacycline (OMC), tetracycline (TET), cephalothin (CEF), clindamycin (CLI), vancomycin (VAN), or linezolid (LZD). Vehicle = 0.0003% DMSO in MH broth. Data represent the mean of 5 cultures; error bars indicate standard deviations. CFU, colony-forming unit; MIC, minimum inhibitory concentration

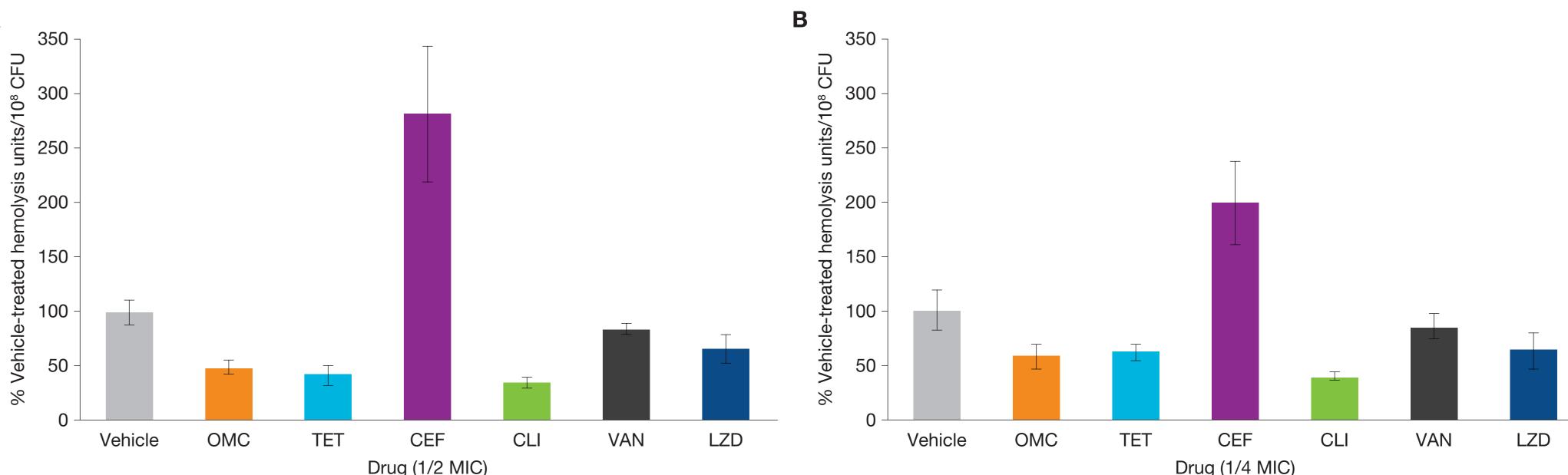
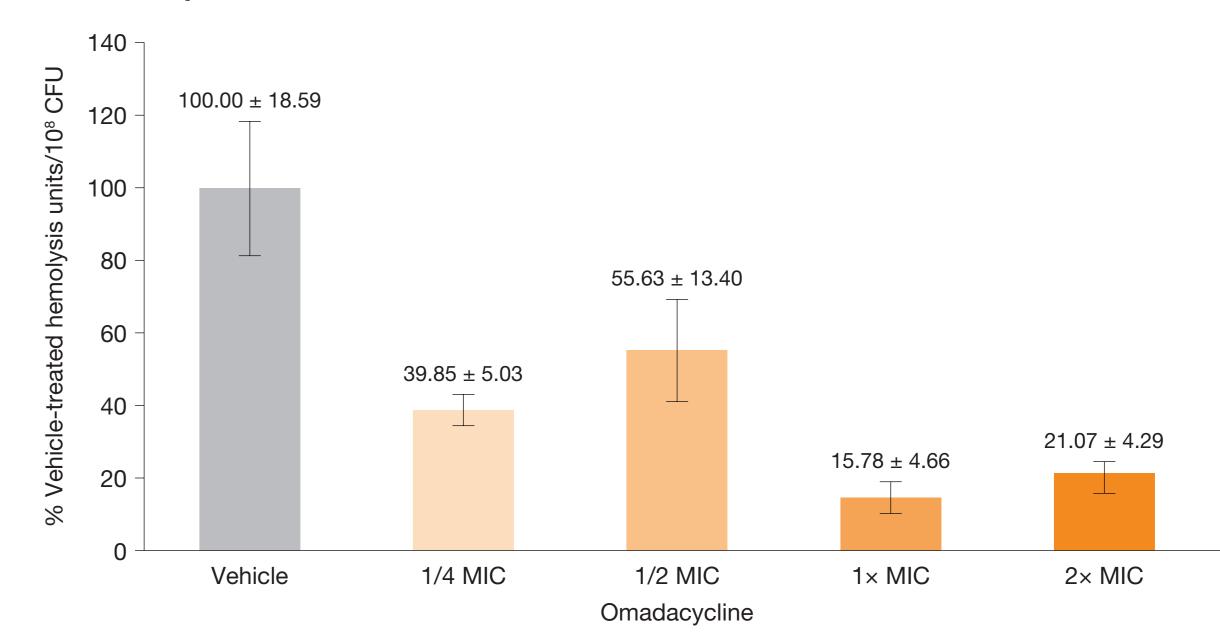


Figure 2: Hemolytic activity of S. aureus Wood 46 grown for 1 hour with the indicated concentration of omadacycline followed by 4 hours' growth without drug. Vehicle = 0.0025% DMSO in MH broth. Data represent the mean of 3 cultures; error bars indicate standard deviations



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