Omadacycline in vitro and in vivo

Omadacycline activity tested against European bacterial isolates from a combined 2010-2011 global surveillance programme

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Background: Omadacycline is a broad spectrum aminomethylcycline in late stage clinical development for the treatment of acute bacterial skin and skin structure infections and community-acquired pneumonia that is being evaluated as both oral and intravenous, once-daily formulations. It has excellent activity against Gram-positive and –negative pathogens including tetracycline resistant organisms. The results from testing omadacycline and comparator agents against clinical isolates collected during 2010-2011 from the European region of a global surveillance study are presented.

Material/methods: More than 20,000 Gram-positive and –negative isolates were selected from patients in 45 medical centers in 14 European countries and Israel. Only one isolate per infection episode per patient was included. A central monitoring laboratory confirmed isolate identity using standard bacteriologic algorithms, the VITEK 2 System, or molecular characterization if necessary. Antibacterial susceptibility testing was performed by broth microdilution per CLSI guidelines. EUCAST breakpoints were used to determine susceptibility rates.

Results: The omadacycline MIC₅₀/₉₀ for all Staphylococcus aureus was 0.12/0.25 mg/L (Table). Against MRSA, omadacycline (MIC₉₀, 0.25 mg/L) and tigecycline (MIC₈₀, 0.25 mg/L; 100.0% susceptible) were the most potent antimicrobials tested while susceptibility to multiple agents including erythromycin (32.9%), clindamycin (67.7%), and levofloxacin (12.0%) were compromised. Omadacycline and tigecycline exhibited potent activity against Enterococcus faecalis and E. faecium (MIC₉₀ values at ≤0.25 mg/L). The MIC₅₀ and MIC₉₀ for omadacycline (0.06/0.06 mg/L) and tigecycline (≤0.03/0.06 mg/L) against Streptococcus pneumoniae, were the lowest among the agents tested and demonstrated activity against ceftriaxone and levofloxacin resistant isolates. Omadacycline and tigecycline MIC values for S. pneumoniae were 16-fold lower than ceftriaxone (MIC₉₀, 1 mg/L) and levofloxacin (MIC₉₀, 1 mg/L). Omadacycline was potent against the β-haemolytic streptococci, MIC₉₀ 0.12 mg/L. All β-haemolytic streptococci were susceptible to tigecycline, β-lactams, linezolid, daptomycin, and vancomycin, however resistance to levofloxacin (95.0% susceptible), erythromycin (81.4% susceptible), clindamycin (92.5% susceptible), tetracycline (45.7% susceptible) and doxycycline (49.5% susceptible) occurred. The MIC₅₀ and MIC₉₀ for omadacycline for the Enterobacteriaceae was 1 and 8 mg/L, respectively. Omadacycline was less potent against Klebsiella pneumoniæ (MIC₅₀/₉₀, 2/8 mg/L [86.8% inhibited at ≤4 mg/L]); ESBL-phenotype MIC₅₀/₉₀, 2/8 mg/L [78.3% inhibited at ≤4 mg/L] and more potent against Escherichia coli (MIC₅₀/₉₀, 0.5/2 mg/L; ESBL-phenotype MIC₅₀/₉₀, 1/4 mg/L [97.9% inhibited at ≤4 mg/L]).

Conclusions: Omadacycline was active against a broad spectrum of Gram-positive and –negative pathogens including MRSA, Enterococci, β-haemolytic streptococci, S. pneumoniae including MDR isolates, and Enterobacteriaceae. Further evaluation in clinical trials is warranted.
<table>
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<th>Select organisms</th>
<th>n</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt;</th>
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<td><em>S. aureus</em></td>
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<td>0.25</td>
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<td>MRSA</td>
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<td>Coagulase negative staphylococci</td>
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<td>1</td>
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