Sulbactam-durlobactam (ETX2514) Is Active Against Recent, Multidrug-Resistant Acinetobacter baumannii Clinical Isolates from the Middle East

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Abstract

Background: The incidence of infections caused by multidrug-resistant (MDR) Acinetobacter baumannii (Ab) (MDR Ab) is increasing at an alarming rate in certain regions of the world, including the Middle East. Ab is intrinsically resistant to multiple classes of antibiotics due to the activity of β-lactamases encoded by R-type plasmids. Concerns have been raised about the emergence and activity of Ab against β-lactam agents. For instance, the presence of β-lactamase inhibitors (like β-lactamase inhibitors (β-LI)) in combination with β-lactam agents can broaden the spectrum of activity against Ab, however, the prevalence of β-LI carriages in Ab has limited its use.

Objective: Durlobactam (DUR, formerly ABT-298) is a double-stranded cyclic diaza[bicyclooctane] (DS-CBO) LI with activity in vitro against MDR Ab – DUR is an antibiotic designed to treat serious infections caused by Acinetobacter, including multidrug-resistant strains, that is currently in Phase 3 clinical development. In global surveillance studies of >3600 isolates from 2012-2017, the MIC90 of Sulbactam (SUL) to its inhibition of PBP3, an enzyme required for cell wall biosynthesis1. However, susceptibility testing of SUL-DUR and combination agents against recent, diverse clinical strains was performed using CLSI and EUCAST breakpoint criteria where available.

Methods: 190 All isolates were collected between 2016 - 2018 from medical centers located in Israel (N = 47), Jordan (N = 30), Qatar (N = 13), Kuwait (N = 42), Lebanon (N = 8), Saudi Arabia (N = 24) and United Arab Emirates (N = 20). Seventy-five percent and 20% of these isolates were from respiratory and blood-stream infections, respectively. Susceptability to SUL-DUR and combination agents was determined by CLSI M100, 30th ed. 2020.

Results: Of the 190 Ab collected, 90% were carbapenem-resistant and 50% combination-based (SUL + CARB) live on a background of 4 mg/L of DUR. The MIC of DUR (and 4 mg/L) decreased the MIC of SUL, from 64 mg/L to 4 mg/L. Only 3 isolates (1.6%) had SUL-DUR MIC values ≤ 4 mg/L. The potency was consistent across countries, sources of infection and resistance of isolates to multiple antibiotics.

Conclusions: SUL-DUR demonstrated potent antibacterial activity against recent clinical isolates of Ab from the Middle East, including MDR isolates. These data support the global development of SUL-DUR for the treatment of MDR Ab infections.

1. Antimicrobial Activity and Whole Genome Sequencing Results for Isolates with Elevated SUL-DUR MIC Values

<table>
<thead>
<tr>
<th>Year</th>
<th>N (isolates)</th>
<th>MIC Range (mg/L)</th>
<th>Resistance Phenotype*</th>
</tr>
</thead>
<tbody>
<tr>
<td>2016</td>
<td>74</td>
<td>≤0.03 - 0.25</td>
<td>Carbapenem-susceptible</td>
</tr>
<tr>
<td>2017</td>
<td>71</td>
<td>≤0.03 - 0.25</td>
<td>Carbapenem-susceptible</td>
</tr>
</tbody>
</table>

*Carbapenem-NS, carbapenem non-susceptible; MDR, multidrug-resistant (non-susceptible to MEM, MIN, AMK); XDR, extremely drug-resistant (NS to MEM, MIN, AMK, CIP, FEP, SUL & R to COL)

1. Background:

Background Information on Ab infections in the Middle East

Methods:

Methods were conducted according to CLSI guidelines using cation-adjusted Mueller-Hinton (CAMH) broth. Sulbactam-durlobactam activity was measured by broth microdilution susceptibility testing according to CLSI M100, 30th ed. 2020. The MIC of SUL-DUR was determined against recent, diverse clinical isolates of Ab collected from seven countries located in the Middle East.

Results:

- The three isolates (3190; 16%) with SUL-DUR MIC values ≥ 8 mg/L were subject to whole genome sequencing.
- All three isolates encoded a mutation near the active site of PBP3, the target of sulbactam inhibition.
- These results are consistent with global surveillance studies of SUL-DUR activity2.

Conclusions:

- Durlobactam restored sulbactam antibacterial activity against a collection of largely drug-resistant A. baumannii clinical isolates collected from countries in the Middle East between 2016 and 2018 with a MIC of 4 mg/L.
- Activity of sulbactam-durlobactam was consistent across seven countries located in the Middle East, years 2016-2018, and sources of infection.
- Less susceptible isolates encoded a mutation in PBP3 (target of sulbactam) and comprised ≥2% of the isolates. These data support development of sulbactam-durlobactam for the treatment of multidrug-resistant A. baumannii.

References