In vitro activity of the siderophore monosulfactam BAL30072 against meropenem-non-susceptible Acinetobacter baumannii

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Objectives: The activity of BAL30072 was compared with that of anti-Acinetobacter reference drugs against meropenem-non-susceptible Acinetobacter baumannii isolates associated with up-regulation of the intrinsic OXA-51-like enzyme or an acquired OXA.

Methods: Antimicrobial susceptibility testing was investigated by broth microdilution of 310 non-duplicate, meropenem-non-susceptible A. baumannii isolates to BAL30072, amikacin ampicillin/sulbactam, aztreonam, cefepime, colistin, imipenem, levofloxacin, meropenem, rifampicin, tigecycline and tobramycin.

Results: BAL30072 showed greater activity than the β-lactam comparators, levofloxacin, amikacin, tobramycin and rifampicin. The activity of BAL30072 was comparable to that of tigecycline, with an MIC₅₀ of 2 mg/L. Elevated BAL30072 MICs were found, but there was no correlation with elevated MICs of the other antimicrobials.

Conclusions: BAL30072 is a promising new agent with good activity against carbapenem-non-susceptible A. baumannii.

Keywords: carbapenems, aztreonam, oxacillinase, tigecycline

Introduction
Multidrug-resistant Acinetobacter baumannii is a growing threat that leaves few therapeutic options. Recently there has been a dramatic increase in carbapenem resistance in A. baumannii mediated mainly through the action of intrinsic and acquired OXA-type enzymes. Metallo-carbapenemases are rare in this species, but potentially pose a significant threat. Drug efflux mechanisms, especially resistance–nodulation–division type (RND) efflux pumps, are involved in resistance to fluoroquinolones, tetracyclines, aminoglycosides and macrolides and have been shown to be overexpressed during antimicrobial therapy. Often colistin is the only antimicrobial to retain activity, but even with this drug resistance develops.

BAL30072 is a novel siderophore monosulfactam currently in Phase I clinical testing. Like the monobactam aztreonam, BAL30072 is stable towards class B metallo-β-lactamases and acts as an inhibitor of class C enzymes; it is also stable towards many class A and class D carbapenemases. BAL30072 has potent activity against a broad range of Gram-negative pathogenic bacteria, including multidrug-resistant A. baumannii. It can enter A. baumannii cells through a non-porin route using endogenous bacterial iron uptake systems, thereby acting like a ‘Trojan horse’ antibiotic.

In this study, the activity of BAL30072 was compared with that of anti-Acinetobacter reference drugs against defined multidrug-resistant, meropenem-non-susceptible A. baumannii isolates that had up-regulation of the intrinsic OXA-51-like enzyme or possessed an acquired OXA.

Materials and methods
Antimicrobial susceptibility testing was performed by broth microdilution in cation-adjusted Mueller–Hinton broth according to CLSI guidelines. BAL30072, amikacin, ampicillin/sulbactam, aztreonam, cefepime, colistin, imipenem, levofloxacin, meropenem, rifampicin, tigecycline and tobramycin were tested against 310 non-duplicate, meropenem-non-susceptible A. baumannii isolates as previously determined by Etest (AB Biodisk, Solna, Sweden). The isolates, collected from over 30 countries, were previously molecularly typed using DiversiLab (bioMérieux, Nürtingen, Germany) and included isolates belonging to worldwide clonal lineages 1–8 (WW1–8) (n = 27, 137, 14, 18, 53, 10, 11 and 7 isolates).
Table 1. MIC distribution, MIC$_{50}$ and MIC$_{90}$ values and percentage susceptibility rates of 310 meropenem-non-susceptible A. baumannii isolates

<table>
<thead>
<tr>
<th>Antimicrobial</th>
<th>≤0.25</th>
<th>0.5</th>
<th>1</th>
<th>2</th>
<th>4</th>
<th>8</th>
<th>16</th>
<th>32</th>
<th>≥64</th>
<th>MIC$_{50}$</th>
<th>MIC$_{90}$</th>
<th>Percentage susceptible</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAM</td>
<td>3</td>
<td>10</td>
<td>42</td>
<td>91</td>
<td>109</td>
<td>55</td>
<td>32</td>
<td>≥64</td>
<td></td>
<td></td>
<td></td>
<td>17.7%</td>
</tr>
<tr>
<td>Imipenem</td>
<td>3</td>
<td>33</td>
<td>55</td>
<td>110</td>
<td>85</td>
<td>24</td>
<td>16</td>
<td>32</td>
<td>≥64</td>
<td></td>
<td></td>
<td>11.6%</td>
</tr>
<tr>
<td>Meropenem</td>
<td>0</td>
<td>15</td>
<td>85</td>
<td>86</td>
<td>124</td>
<td>32</td>
<td>32</td>
<td>0</td>
<td></td>
<td></td>
<td></td>
<td>0%</td>
</tr>
<tr>
<td>Cefepime</td>
<td>1</td>
<td>13</td>
<td>45</td>
<td>251</td>
<td>≥64</td>
<td>≥64</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aztreonam</td>
<td>0</td>
<td>3</td>
<td>61</td>
<td>246</td>
<td>≥64</td>
<td>≥64</td>
<td>0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BAL30072</td>
<td>15</td>
<td>29</td>
<td>53</td>
<td>59</td>
<td>27</td>
<td>18</td>
<td>13</td>
<td>77</td>
<td>2</td>
<td>≥64</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Levofloxacin</td>
<td>2</td>
<td>1</td>
<td>4</td>
<td>13</td>
<td>75</td>
<td>77</td>
<td>72</td>
<td>66</td>
<td>16</td>
<td>≥64</td>
<td></td>
<td>3.3%</td>
</tr>
<tr>
<td>Amikacin</td>
<td>18$^b$</td>
<td>27</td>
<td>17</td>
<td>24</td>
<td>31</td>
<td>52</td>
<td>141</td>
<td>32</td>
<td>≥256</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tobramycin</td>
<td>24</td>
<td>40</td>
<td>22</td>
<td>17</td>
<td>24</td>
<td>26</td>
<td>38</td>
<td>36</td>
<td>83</td>
<td>16</td>
<td>≥64</td>
<td>4.1%</td>
</tr>
<tr>
<td>Tigecycline</td>
<td>2</td>
<td>24</td>
<td>62</td>
<td>134</td>
<td>63</td>
<td>23</td>
<td>2</td>
<td>2</td>
<td>4</td>
<td>28.4$^c$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rifampicin</td>
<td>1</td>
<td>3</td>
<td>21</td>
<td>191</td>
<td>35</td>
<td>5</td>
<td>6</td>
<td>48</td>
<td>4</td>
<td>≥128</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>118</td>
<td>146</td>
<td>43</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.5</td>
<td>1</td>
<td>100%</td>
</tr>
</tbody>
</table>

NBS, no breakpoint set.
Susceptible breakpoint values are indicated in bold.
SAM, ampicillin/sulbactam at a ratio of 2:1; MIC value refers to ampicillin.
$^b$CLSI breakpoint for P. aeruginosa.
$^c$MIC ≤1 mg/L.
$^d$EUCAST breakpoint for Enterobacteriaceae.

respectively) and unclustered isolates (n=33). WW1–3 correspond to European clonal complexes I–III, respectively. Isolates were characterized for their carbapenem resistance mechanisms. They included 120 strains with overexpression of the intrinsic bla$_{OXA-51}$ due to the presence of ISAb1 adjacent to the gene, 89 strains with bla$_{OXA-23}$, 22 strains with bla$_{OXA-40}$, 73 strains with bla$_{OXA-58}$ and 2 strains with bla$_{OXA-143}$. In addition, eight isolates had overexpression of bla$_{OXA-51}$ in addition to an acquired bla$_{OXA}$, two isolates possessed both bla$_{OXA-23}$ and bla$_{OXA-58}$, and two isolates had an as yet uncharacterized carbapenem resistance mechanism.

Results and discussion

MIC distribution, MIC$_{50}$ and MIC$_{90}$ values and percentage susceptibility rates are summarized in Table 1. All isolates were non-susceptible to meropenem and aztreonam, and all isolates but one were non-susceptible to cefepime. All isolates were susceptible to meropenem and aztreonam, and all isolates but 89% of carbapenem-resistant A. baumannii have been reported in all parts of the world with ever-increasing frequency. In particular, it is the development of carbapenem resistance that has left clinicians with few viable alternatives. Colistin is often the only antimicrobial showing measurable activity, but owing to toxicity and low serum concentrations it is not always effective. Over the last decade there have been few novel anti-Gram-negative drugs developed. Much effort has gone into the development of anti-Gram-positive drugs, which has left the door open for multidrug-resistant organisms such as A. baumannii. Tigecycline is one of few new drugs with activity against Acinetobacter that has made it to the market, although it is associated with a number of clinical side effects, resistance development and breakthrough bacteraemia. However, even with such a new drug, elevated MICs for A. baumannii have been reported, mediated by efflux and sometimes without prior exposure to the drug. There is therefore a need for new drugs that are unaffected by the current β-lactamases and efflux pumps. In a previous study, 89% of carbapenem-resistant A. baumannii had BAL30072 MICs of ≤8 mg/L whereas in our study it was 65%. In the former study, 85% of isolates belonged to the so-called OXA-23 clone 1 and SE clone, which represent European clonal lineage II. Additionally, in the former study 50% of isolates with BAL30072 MICs ≥16 mg/L were not part of this clonal complex, suggesting that the clone of the OXA-23 clone 1/SE clone may have impacted on the data on susceptibility to BAL30072. This is illustrated in the MIC$_{50}$ and MIC$_{90}$ values, which were 0.5 and 4 mg/L for European clonal lineage II (OXA-23 clone 1 and SE clones) and 4 and ≥128 mg/L for the ‘other A. baumannii clones’, respectively. In our study, MIC$_{50}$ and MIC$_{90}$ values were higher (2 and ≥64 mg/L, respectively).

There is an ever-increasing need for the development of new drugs that show anti-Acinetobacter activity. Outbreaks caused by multidrug-resistant A. baumannii have been reported in all parts of the world. In particular, it is the development of carbapenem resistance that has left clinicians with few viable alternatives. Colistin is often the only antimicrobial showing measurable activity, but owing to toxicity and low serum concentrations it is not always effective. Over the last decade there have been few novel anti-Gram-negative drugs developed. Much effort has gone into the development of anti-Gram-positive drugs, which has left the door open for multidrug-resistant organisms such as A. baumannii. Tigecycline is one of few new drugs with activity against Acinetobacter that has made it to the market, although it is associated with a number of clinical side effects, resistance development and breakthrough bacteraemia. However, even with such a new drug, elevated MICs for A. baumannii have been reported, mediated by efflux and sometimes without prior exposure to the drug. There is therefore a need for new drugs that are unaffected by the current β-lactamases and efflux pumps. In a previous study, 89% of carbapenem-resistant A. baumannii had BAL30072 MICs of ≤8 mg/L whereas in our study it was 65%. In the former study, 85% of isolates belonged to the so-called OXA-23 clone 1 and SE clone, which represent European clonal lineage II. Additionally, in the former study 50% of isolates with BAL30072 MICs ≥16 mg/L were not part of this clonal complex, suggesting that the clone of the OXA-23 clone 1/SE clone may have impacted on the data on susceptibility to BAL30072. This is illustrated in the MIC$_{50}$ and MIC$_{90}$ values, which were 0.5 and 4 mg/L for European clonal lineage II (OXA-23 clone 1 and SE clones) and 4 and ≥128 mg/L for the ‘other A. baumannii clones’, respectively. In our study, MIC$_{50}$ and MIC$_{90}$ values were higher (2 and ≥64 mg/L, respectively).
for isolates representing the clonal lineages WW1, WW2, WW3, WW6 and WW7, and unclustered isolates. MIC\textsubscript{50}/MIC\textsubscript{90} values for WW4, WW5 and WW8 isolates were 1/16, 8/≥64 and 1/2 mg/L, respectively. There are few in vivo data regarding BAL30072. A recent study showed that a BAL30072/meropenem combination resulted in a lowering of MICs of between 2- and 8-fold, and in a rat model BAL30072 was active against meropenem-susceptible and -resistant A. baumannii.\textsuperscript{18}

In conclusion, BAL30072, currently in Phase I clinical testing, is a promising new agent with good activity against carbapenem-non-susceptible A. baumannii and has the potential to become a useful addition to the limited armamentarium of drugs that can be used to treat this problem pathogen.

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**Transparency declarations**
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**References**