TP-6076 was active against bacterial isolates carrying emergent resistance traits
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Abstract

Background. Transferable and mutation-based resistance amongst clinically relevant Gram-negative pathogens remains an ongoing impediment to the development of novel antimicrobial therapies. While there are a number of new agents in development for the treatment of multidrug-resistant and carbapenem-resistant Enterobacteriaceae (CRE) and Acinetobacter baumannii (CRAB), coverage gaps due to resistance persist. TP-6076 was screened against a number of Enterobacteriaceae and Acinetobacter isolates from the CDC antimicrobial resistance bank and clinical sources as a proof-of-concept for activity against various resistance types. TP-6076 was assayed for activity against isolates carrying various RNA methylase genes, genes encoding fosfomycin resistance, tetracycline efflux pump genes, porin mutations, and those isolates resistant to cefazolin-avibactam (CAZ-AV). Methods. Susceptibility testing by both broil microdilution minimal inhibitory concentration (MIC) assays was done using CLSI methodology. Isolates screened were selected from the CDC Antimicrobial Resistance Bank panels and the laboratory of Patrice Nordmann. Isolates resistance information was provided by the CDC whole genome sequencing data (RNA methylase, porin mutation, fosfomycin resistance) or PCR and sequencing performed for this study. Results. The TP-6076 MIC<sub>50</sub> values for total Enterobacteriaceae, total Acinetobacter, and resistance subgroups are presented in the Table. Overall, TP-6076 MIC<sub>50</sub> values for resistant pathogens remained within one dilution of the MIC<sub>50</sub> value, with the exception of Enterobacter cloacae, which had a MIC<sub>50</sub> of 0.016/0.063 µg/ml for Enterobacteriaceae and 0.016/0.063 µg/ml for A. baumannii. Conclusions. TP-6076 retained potency in vitro against a number of emergent resistance types and represents a promising candidate in development for the treatment of multidrug-resistant Gram-negative pathogens.

Table 1. TP-6076 activity against total and resistant subgroups of Enterobacteriaceae

| Enterobacteriaceae | MIC<sub>50</sub> range | Total Enterobacteriaceae | CRAB | CRE | Other | CNABER | CAMB | CAZ-AV | CAZ
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<tbody>
<tr>
<td>Tetracycline</td>
<td>0.004 – 0.25</td>
<td>0.016 – 0.063</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Minocycline</td>
<td>0.004 – 0.25</td>
<td>0.016 – 0.063</td>
<td>4</td>
<td>2</td>
<td>0</td>
<td>0</td>
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Background

Transferable and mutation-based resistance amongst clinically relevant Gram-negative pathogens remains an ongoing impediment to the development of novel antimicrobial therapies. While there are a number of new agents in development for the treatment of multidrug-resistant and carbapenem-resistant Enterobacteriaceae (CRE) and Acinetobacter baumannii (CRAB), coverage gaps due to resistance persist. Novel antimicrobial agents in the aminoglycoside class have been shown to be hindered in activity against CRE due to transferable aminoglycoside resistance (37), while the carbapenem class has been reported to be hindered in activity against CRAB due to tetracycline resistance (37). Isolates screened were selected from the CDC Antimicrobial Resistance Bank panels and the laboratory of Patrice Nordmann. Isolates resistance information was provided by the CDC whole genome sequencing data (RNA methylase, porin mutation, fosfomycin resistance) or PCR and sequencing performed for this study.

Results.

Materials / Methods

Suscetibility testing by both microdilution minimal inhibitory concentration (MIC) assays was done using CLSI methodology (8). Isolates screened were selected from the CDC Antimicrobial Resistance Bank panels and the laboratory of Patrice Nordmann (University of Fribourg). CDC panel isolates for this study were combined from the Enterobacteriaceae Carbapenem Resistant Bank and the laboratory of Dr. Patrice Nordmann (University of Fribourg). The MIC<sub>50</sub> values for total Enterobacteriaceae, total Acinetobacter, and resistance subgroups are presented in the Table. Overall, TP-6076 MIC<sub>50</sub> values for resistant pathogens remained within one dilution of the MIC<sub>50</sub> value, with the exception of Enterobacter cloacae, which had a MIC<sub>50</sub> of 0.016/0.063 µg/ml for Enterobacteriaceae and 0.016/0.063 µg/ml for A. baumannii.

Conclusions.

TP-6076 retained potency in vitro against a number of emergent resistance types and represents a promising candidate in development for the treatment of multidrug-resistant Gram-negative pathogens.

References