Cefepime-Zidebactam (WCK 5222) Activity against Clinical Isolates of Non-Fermentative Gram-Negative Bacilli Collected Worldwide in 2018

Helio S. Sader, Cecilia G. Carvalhaes, Leonard R. Duncan, S.J. Ryan Arends, Rodrigo E. Mendes, Mariana Castanheira
JMI Laboratories, North Liberty, Iowa, USA

Introduction

• Zidebactam is a non-beta-lactam agent with a dual mechanism of action: selective and high-affinity gram-negative penicillin-binding protein (PBP) 2 binding and beta-lactamase inhibition.

• Zidebactam demonstrates antibacterial activity against various Enterobacteriales isolates and non-fermentative gram-negative bacilli (NF-GNB) due to PBP2 binding

• Cefepime-zidebactam is in clinical development at Cephalon, Inc.

• The cefepime susceptible breakpoint of ≤8 mg/L for comparison purposes only, and a cefepime-zidebactam pharmacokinetic/pharmacodynamic breakpoint, for comparison purposes; the highest MIC was ≤8 mg/L for all global isolates inhibited at ≤32 mg/L (Table 1)

Materials and Methods

• A total of 3,711 NF-GNB isolates were collected by the 2018 SENTINEL Antimicrobial Surveillance Program, including:
  - Pseudomonas aeruginosa: 2,719 isolates
  - Acinetobacter spp.: 624 isolates
  - Stenotrophomonas maltophilia: 326 isolates
  - Burkholderia cepacia: 42 isolates

• Susceptibility testing was performed in a central laboratory by a research for minimum inhibitory concentration method against cefepime-zidebactam (1:1 ratio) and comparators

• The cefepime susceptible breakpoint of ≤8 mg/L (CLSI, high dose) was applied for cefepime-zidebactam for comparison purposes only, and a cefepime-zidebactam susceptible breakpoint of ≤32 mg/L has been proposed based on pharmacokinetic/pharmacodynamic target attainment and was applied for NF-GNB

• CLSI breakpoints were applied for comparators, when available

• Multiring-resistant (MDR) and extensively drug-resistant (XDR) P. aeruginosa strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows
  - MDR: 3 or more drug classes have a nonsusceptible drug
  - XDR: all but 2 or fewer classes have a nonsusceptible drug

Results

• Cefepime-zidebactam exhibited potent activity against P. aeruginosa (MIC90 ≤4/8 mg/L) with 99.0% (Asia-Pacific region [APAC]) to 100.0% (Latin America [LATAM]) of isolates inhibited at ≤8 mg/L and 100.0% of all global isolates inhibited at ≤32 mg/L (Table 1 and Figure 1)

• P. aeruginosa susceptibility rates for ceftepime-avibactam, cefepime-zidebactam, cefepime-tazobactam, and meropenem were 95.0%, 94.9%, 76.3%, and 76.5%, respectively (Table 1)

• Cefepime-zidebactam retained potent activity against MDR P. aeruginosa (MIC90 ≤4/8 mg/L; 96.5%/100.0% inhibited at ≤8/≤64 mg/L) and XDR (MIC90 ≤4/8 mg/L; 91.0%/100.0% inhibited at ≤8/≤64 mg/L) (Table 1)

• Cefepime-zidebactam inhibited 92.8% of ceftolozane-tazobactam-nonsusceptible (n=135) isolates at ≤8 mg/L (highest MIC, 32 mg/L)

• Against Acinetobacter spp., percentages inhibited at ≤8/≤16 mg/L of cefepime-zidebactam were 73.4/99.4% in the USA, 44.9/99.2% in Europe (EUR), 59.1/100.0% in APAC and 29.8/100.0% in LATAM, and mepenem susceptibility rates were 69.9%, 24.2%, 43.2% and 8.3% in the USA, EUR, APAC, and LATAM, respectively (Table 2)

• Cefepime-zidebactam inhibited 76.7% (EUR) to 100.0% (LATAM) of A. cepacia isolates at ≤8 mg/L and 99.4% (USA) to 100.0% (EUR, APAC, and LATAM) at ≤64 mg/L (Table 3)

• Against B. cepacia overall, 88.1% were inhibited at ≤8 mg/L cefepime-zidebactam and 100.0% were inhibited at ≤8 mg/L meropenem (Table 3)

Conclusions

• Cefepime-zidebactam demonstrated potent in vitro activity against contemporary isolates of non-fermentative bacilli collected worldwide in 2018

• Cefepime-zidebactam retained good activity against MDR and XDR P. aeruginosa isolates, including most isolates nonsusceptible to cefepime-tazobactam and/or ceftazidime-avibactam

• These in vitro results support further development of cefepime-zidebactam for treatment of systemic infections caused by NF-GNB

Materials and Methods

• A total of 3,711 NF-GNB isolates were collected by the 2018 SENTINEL Antimicrobial Surveillance Program, including:
  - Pseudomonas aeruginosa: 2,719 isolates
  - Acinetobacter spp.: 624 isolates
  - Stenotrophomonas maltophilia: 326 isolates
  - Burkholderia cepacia: 42 isolates

• Susceptibility testing was performed in a central laboratory by a reference broth microdilution method according to cefepime-zidebactam (1:1 ratio) and comparators

• The cefepime susceptible breakpoint of ≤8 mg/L (CLSI, high dose) was applied for cefepime-zidebactam for comparison purposes only, and a cefepime-zidebactam susceptible breakpoint of ≤32 mg/L has been proposed based on pharmacokinetic/pharmacodynamic target attainment and was applied for NF-GNB

• CLSI breakpoints were applied for comparators, when available

• Multiring-resistant (MDR) and extensively drug-resistant (XDR) P. aeruginosa strains were classified according to recommended guidelines (Magiorakos et al., 2012) as follows
  - MDR: 3 or more drug classes have a nonsusceptible drug
  - XDR: all but 2 or fewer classes have a nonsusceptible drug

Table 1 Activity of cefepime-zidebactam and comparator antimicrobial agents when tested against 2,719 Pseudomonas aeruginosa isolates collected worldwide during 2018

<table>
<thead>
<tr>
<th>Antimicrobial agent</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (mg/L)</th>
<th>% susceptible&lt;sup&gt;a&lt;/sup&gt; (no. of isolates)</th>
</tr>
</thead>
<tbody>
<tr>
<td>USA</td>
<td>EUR</td>
<td>APAC</td>
</tr>
<tr>
<td>Cefepime-zidebactam</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>Cefepime-tazobactam</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Meropenem</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>8</td>
<td>8</td>
</tr>
</tbody>
</table>

Abbreviations: %S, percentage susceptible; TMP-SMX, trimethoprim-sulfamethoxazole; NT, not tested.

Abbreviations: USA, United States of America; EUR, Europe; APAC, Asia-Pacific region; LATAM, Latin America; MDR, multidrug-resistant; XDR, extensively drug-resistant.

Conclusions

• Cefepime-zidebactam demonstrated potent in vitro activity against contemporary isolates of non-fermentative bacilli collected worldwide in 2018

• Cefepime-zidebactam retained good activity against MDR and XDR P. aeruginosa isolates, including most isolates nonsusceptible to cefepime-tazobactam and/or ceftazidime-avibactam

• These in vitro results support further development of cefepime-zidebactam for treatment of systemic infections caused by NF-GNB

Acknowledgements

This study was supported by Wockhardt Bio AG.

Contact

To obtain a PDF of this poster:
Scan the QR code or visit https://www.jmilabs.com/data/posters


Charges may apply. No personal information is stored.