Characteristics and Outcomes of Complicated Intra-abdominal Infections Involving *Pseudomonas aeruginosa* from a Randomized, Double-Blind, Phase 3 Ceftolozane-Tazobactam Study

Benjamin Miller, a Myra W. Popejoy, b Ellie Hershberger, a Judith N. Steenbergen, b John Alverdy c

Department of Medical Affairs, Merck & Co., Inc., Kenilworth, New Jersey, USA a; Merck Research Laboratories, Merck & Co., Inc., Kenilworth, New Jersey, USA b; Department of Surgery, University of Chicago Medical Center, Chicago, Illinois, USA c

Ceftolozane-tazobactam is active against Gram-negative pathogens, including multidrug-resistant *Pseudomonas aeruginosa*. In a subgroup analysis of patients with complicated intra-abdominal infections (cIAIs) involving *P. aeruginosa* from a phase 3 program, ceftolozane-tazobactam demonstrated potent in vitro activity against *P. aeruginosa*. Clinical cure in the microbiologically evaluable population was 100% (26/26) for ceftolozane-tazobactam plus metronidazole and 93.1% (27/29) for meropenem. These findings support the use of ceftolozane-tazobactam in the management of cIAI when *P. aeruginosa* is suspected or confirmed. (This study has been registered at ClinicalTrials.gov under registration no. NCT01445665 and NCT01445678.)

C omplicated intra-abdominal infections (cIAIs) are caused by Gram-negative bacteria, with *Enterobacteriaceae* being the most common pathogen. *Pseudomonas aeruginosa* is the third-most-common Gram-negative bacteria in cIAI (1), and increasing rates of *P. aeruginosa* resistance are a global concern (2, 3).

Ceftolozane-tazobactam, in combination with metronidazole, is approved for the treatment of cIAI (4). Ceftolozane-tazobactam has potent activity against many drug-resistant Gram-negative pathogens, including most extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae* (5, 6), and is minimally affected by common *P. aeruginosa* resistance mechanisms (7). Compared with approved β-lactam antibiotics, including meropenem and piperacillin-tazobactam, ceftolozane-tazobactam displays more potent in vitro activity against *P. aeruginosa* (8).

The Assessment of the Safety Profile and Efficacy of Ceftolozane/Tazobactam in Complicated Intra-Abdominal Infections (ASPECT-cIAI) study was a global phase 3 program that demonstrated the efficacy of ceftolozane-tazobactam plus metronidazole to be similar to that of meropenem in patients with cIAI (NCT01445665 and NCT01445678) (9). This analysis was conducted to determine the characteristics and clinical outcomes of the subgroup of patients with *P. aeruginosa* infection.

(Var of this research was presented as poster 251 at IDWeek, the annual meeting of the Infectious Diseases Society of America [IDSA], the Society for Healthcare Epidemiology of America [SHEA], the HIV Medicine Association [HIVMA], and the Pediatric Infectious Diseases Society [PIDS], 8 to 12 October 2014, Philadelphia, PA.)

In ASPECT-cIAI, patients (age, ≥18 years) with cIAI were randomly assigned 1:1 to receive intravenous ceftolozane-tazobactam (1.5 g containing 1,000 mg ceftolozane and 500 mg tazobactam) plus metronidazole (500 mg) every 8 h or intravenous meropenem (1 g every 8 h) plus placebo for 4 to 14 days. Efficacy was assessed at the test-of-cure visit 24 to 32 days after initiation of the study drug. Clinical cure was defined as the resolution of or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or intervention was necessary. Descriptive statistics were used to compare baseline characteristics (microbiological intent-to-treat [MITT] population) and clinical outcomes (microbiologically evaluable [ME] population) of patients with and without *P. aeruginosa* infection. Descriptions of inclusion/exclusion criteria and study design were published previously (9).

MIC cutoffs for susceptibility to ceftolozane-tazobactam and meropenem were based on Clinical and Laboratory Standards Institute (CLSI) definitions (10). Multidrug resistance (MDR) in *P. aeruginosa* was based on CLSI breakpoints and defined as nonsusceptibility to ≥3 drug classes known to be active against *P. aeruginosa*. *P. aeruginosa* isolates were screened for AmpC overexpression.

In the MITT population, 8.9% (72/806) of patients had *P. aeruginosa* infection at baseline; 4 patients had *P. aeruginosa* as the only infecting pathogen. Baseline demographic characteristics were similar between patients with and those without *P. aeruginosa* infection (Table 1). *P. aeruginosa* infection was more frequent in North America (17.6% [9/51]) than in Europe (7.9% [50/635]) and more commonly isolated in patients with colonic (14.4% [7/118]) or appendicular (11.2% [43/384]) infections. In patients with *P. aeruginosa* infection, 65.3% (47/72) received previous antibacterial therapy, compared with 56.8% (417/734) of patients without *P. aeruginosa* infection. Previous therapies included metronidazole (41.7%), ceftriaxone (12.5%), and cefotaxime (8.3%); mean duration of therapy (7.8 days) was the same.
TABLE 1 Baseline demographics of all patients in the ASPECT-cIAI trial (microbiological intent-to-treat population)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>P. aeruginosa at baseline (n = 72)</th>
<th>No P. aeruginosa at baseline (n = 734)</th>
<th>Total (n = 806)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male (n [%])</td>
<td>48 (66.7)</td>
<td>418 (56.9)</td>
<td>466 (57.8)</td>
</tr>
<tr>
<td>Race, white (n [%])</td>
<td>63 (87.5)</td>
<td>692 (94.3)</td>
<td>755 (93.7)</td>
</tr>
<tr>
<td>Mean age (SD) (yr)</td>
<td>49.5 (19.3)</td>
<td>50.7 (17.4)</td>
<td>50.6 (17.5)</td>
</tr>
<tr>
<td>≥75 yr (n [%])</td>
<td>8 (11.1)</td>
<td>75 (10.2)</td>
<td>83 (10.3)</td>
</tr>
<tr>
<td>Mean body mass index (SD) (kg/m²)</td>
<td>27.1 (6.3)</td>
<td>26.9 (5.3)</td>
<td>26.9 (5.4)</td>
</tr>
<tr>
<td>Baseline APACHE II score category (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10</td>
<td>61 (84.7)</td>
<td>596 (81.2)</td>
<td>657 (81.5)</td>
</tr>
<tr>
<td>≥10</td>
<td>11 (15.3)</td>
<td>137 (18.7)</td>
<td>148 (18.4)</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min) (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal (≥80)</td>
<td>47 (65.3)</td>
<td>516 (70.3)</td>
<td>563 (69.9)</td>
</tr>
<tr>
<td>Mild renal impairment (≥50 to &lt;80)</td>
<td>24 (33.3)</td>
<td>183 (24.9)</td>
<td>207 (25.7)</td>
</tr>
<tr>
<td>Moderate renal impairment (≥30 to ≤50)</td>
<td>1 (1.4)</td>
<td>35 (4.8)</td>
<td>36 (4.5)</td>
</tr>
<tr>
<td>Geographic origin (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Europe</td>
<td>50 (69.4)</td>
<td>585 (79.7)</td>
<td>635 (78.8)</td>
</tr>
<tr>
<td>North America</td>
<td>9 (12.5)</td>
<td>42 (5.7)</td>
<td>51 (6.3)</td>
</tr>
<tr>
<td>South America</td>
<td>6 (8.3)</td>
<td>75 (10.2)</td>
<td>81 (10.0)</td>
</tr>
<tr>
<td>Rest of world</td>
<td>7 (9.7)</td>
<td>32 (4.4)</td>
<td>39 (4.8)</td>
</tr>
<tr>
<td>Anatomic site of infection (n [%])</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appendix</td>
<td>43 (59.7)</td>
<td>341 (46.5)</td>
<td>384 (47.6)</td>
</tr>
<tr>
<td>Biliary cholecystitis/cholangitis</td>
<td>5 (6.9)</td>
<td>138 (18.8)</td>
<td>143 (17.7)</td>
</tr>
<tr>
<td>Stomach/duodenum</td>
<td>4 (5.6)</td>
<td>75 (10.2)</td>
<td>79 (9.8)</td>
</tr>
<tr>
<td>Colon</td>
<td>17 (23.6)</td>
<td>101 (13.8)</td>
<td>118 (14.6)</td>
</tr>
<tr>
<td>Small bowel</td>
<td>1 (1.4)</td>
<td>41 (5.6)</td>
<td>42 (5.2)</td>
</tr>
<tr>
<td>Parenchymal (liver)</td>
<td>1 (1.4)</td>
<td>32 (4.4)</td>
<td>33 (4.1)</td>
</tr>
<tr>
<td>Parenchymal (spleen)</td>
<td>0</td>
<td>4 (0.5)</td>
<td>4 (0.5)</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1.4)</td>
<td>15 (2.0)</td>
<td>16 (2.0)</td>
</tr>
</tbody>
</table>

aData missing for 1 patient. APACHE II, Acute Physiology and Chronic Health Evaluation II.

for patients with and those without P. aeruginosa infection. In total, 8.9% (4/5) of patients for whom previous antibacterial therapy was ineffective (amoxicillin-clavulanic acid and ertapenem; cefotaxime, metronidazole, and piperacillin-tazobactam; metronidazole and cefuroxime axetil; and metronidazole, ceftriaxone sodium, and cefuroxime axetil) had P. aeruginosa infection.

Most P. aeruginosa (97.2% [70/72]) and non-P. aeruginosa (92.9% [682/734]) infections were community acquired, and P. aeruginosa was more likely to be isolated as part of a polymicrobial infection (94.4% [68/72]). All three cases of concurrent bactemia in patients with P. aeruginosa occurred with polymicrobial infections; bacteremia was a result of Propionibacterium acnes, Eggerthella lenta, and Enterococcus faecalis infection, and all patients were deemed to be clinically cured.

Both ceftolozane-tazobactam and meropenem were highly active in vitro against P. aeruginosa, with an MIC required to inhibit the growth of 90% of isolates (MIC₉₀) of 2 μg/ml for ceftolozane-tazobactam and 4 μg/ml for meropenem. Cefotolozane-tazobactam was the most potent agent tested; 97.1% of isolates were inhibited at an MIC of ≤4 μg/ml, whereas susceptibility to meropenem was 89.9% (Fig. 1A). Based on MIC₉₀ values, ceftolozane-tazobactam (MIC₉₀ 2 μg/ml) was 32-fold more active than piperacillin-tazobactam (MIC₉₀ 64 μg/ml) and 8-fold more active than ceftriaxime, cefepime, aztreonam, or gentamicin (MIC₉₀ 16 μg/ml for each).
All patients in the ME population with P. aeruginosa infection had a 100% clinical cure rate with ceftolozane-tazobactam plus metronidazole. In this study of primarily community-acquired cIAIs, the prevalence of MDR P. aeruginosa was low; nevertheless, ceftolozane-tazobactam had potent \textit{in vitro} activity against P. aeruginosa (MIC$_{90}$, 0.008–0.016 \(\mu\)g/ml). Because of the small number of patients in this nonrandomized subgroup analysis, the summary of data might have been subject to bias.

Ceftolozane-tazobactam plus metronidazole was effective in AmpC-overexpressing strains of P. aeruginosa, consistent with \textit{in vitro} studies that have shown ceftolozane’s stability against P. aeruginosa resistance mechanisms, including hydrolysis by AmpC enzymes, upregulation of efflux pumps, and decreases in porin expression (7, 17, 18).

Ceftolozane-tazobactam has been shown to be active against strains of P. aeruginosa that are resistant to carbapenems, piperacillin-tazobactam, cephalosporins, fluoroquinolones, and aminoglycosides, including the majority of MDR isolates (17, 19, 20), with the exception of metallo-\(\beta\)-lactamases. The ASPECT-cIAI findings suggest that ceftolozane-tazobactam will be an important

\begin{table}[h]
\centering
\caption{\textit{In vitro} activity of ceftolozane-tazobactam and comparator antibacterials against AmpC-producing and MDR P. aeruginosa isolates identified at screening visit (microbiologically evaluable population)}
\label{tab:in vitro activity}
\begin{tabular}{llccccccccc}
\hline
Treatment group & Clinical outcome & MIC (\(\mu\)g/ml) & & & & & & & & \\
& & Ceftolozane-tazobactam & Meropenem & Aztreonam & Cefepime & Ceftazidime & Gentamicin & Piperacillin-tazobactam & & \\
AmpC producers (n = 10) & & & & & & & & & & \\
Ceftolozane-tazobactam & Cure & 0.5 & 1 & 4 & 2 & 2 & 1 & 8 & & \\
Ceftolozane-tazobactam & Cure & 1 & 0.5 & 8 & 2 & 4 & 2 & 16 & & \\
Ceftolozane-tazobactam & Cure & 1 & 1 & 8 & 4 & 4 & 2 & 8 & & \\
Ceftolozane-tazobactam & Cure & 2 & 2 & 8 & 16 & 16 & >16 & 64 & & \\
Ceftolozane-tazobactam & Cure & 1 & 4 & 4 & 4 & 4 & 2 & 8 & & \\
Meropenem* & Cure & 4 & 2 & 16 & 16 & 16 & >16 & 128 & & \\
Meropenem & Cure & 1 & 0.5 & 4 & 4 & 4 & 1 & 8 & & \\
Meropenem & Cure & 1 & 0.25 & 0.5 & 2 & 1 & 2 & >0.25 & & \\
Meropenem & Cure & 16 & 2 & 32 & 32 & >32 & >16 & >128 & & \\
Meropenem & Cure & 4 & 4 & >32 & 32 & >32 & 16 & >128 & & \\
MDRb (n = 3) & & & & & & & & & & \\
Meropenem* & Cure & 4 & 2 & 16 & 16 & 8 & >16 & 128 & & \\
Meropenem & Cure & 16 & 2 & 32 & 32 & >32 & >16 & >128 & & \\
Meropenem & Cure & 4 & 4 & >32 & 32 & >32 & 16 & >128 & & \\
\hline
\multicolumn{11}{l}{* Isolate was positive for AmpC and MDR.} \\
\multicolumn{11}{l}{b MDR was based on CLSI breakpoints and defined as nonsusceptibility to \(\geq 3\) drug classes that are known to be active against P. aeruginosa.}
\end{tabular}
\end{table}
addition to the available antibacterials used in the treatment of cIAIs, especially when *P. aeruginosa* is implicated.

**ACKNOWLEDGMENTS**

This study was funded by Merck & Co., Inc., Kenilworth, NJ, USA.

Medical writing and editorial assistance was provided by Tracy T. Cao and Meryl Mandle from ApotheCom, Yardley, PA, USA. This assistance was funded by Merck & Co., Inc.

M.W.P. is an employee and B.M., E.H., and J.N.S. are former employees of Merck & Co., Inc., Kenilworth, NJ, USA. J.A. has participated in advisory boards for Cubist Pharmaceuticals.

We and employees of the study sponsor were involved in the study design, data collection, and interpretation and in the decision to submit the work for publication.

**FUNDING INFORMATION**

This work, including the efforts of Myra Popejoy, was funded by Merck (Merck & Co., Inc.).

**REFERENCES**


