Activity of cephalosporin CXA-101 (FR264205) and comparators against extended-spectrum-β-lactamase-producing Pseudomonas aeruginosa

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Sir,

Extended-spectrum-β-lactamases (ESBLs), belonging to Ambler classes A and D, or ESBL_A and ESBL_M-D according to the recently suggested novel classification,1 are sometimes encountered in Pseudomonas aeruginosa.2 Although the consequences of the emergence of metallo-β-lactamasmes (MBLs; ESBLcarbA-B) are even more devastating, the emergence of ESBL_A and ESBL_M-D (oxacilinases) in P. aeruginosa still poses a substantial therapeutic challenge. Also, piperacillin/tazobactam has been found to have limited activity against ESBL_A-producing P. aeruginosa.2 Recently, the cephalosporin CXA-101 (Calixa Therapeutics Inc., San Diego, CA, USA) has completed Phase I trials and in vitro this agent has been found to have excellent antipseudomonal activity,3 but no data are currently available on the activity of this agent, with and without β-lactamase inhibitors, against characterized clinical isolates of ESBL-producing P. aeruginosa.

A collection of previously characterized ESBL_A-producing (n=9) and ESBL_M-D-producing (n=1) P. aeruginosa was obtained from Hôpital de Bicêtre, Paris, France. The collection consisted of 10 clinical isolates of P. aeruginosa producing the β-lactamases GES-2, GES-9, VEB-1, VEB-1-A, PER-1, BEL-1, SHV-2a, SHV-5, TEM-4 and OXA-32.2,4-6 The clinical isolates were subjected to antimicrobial susceptibility testing by broth microdilution (Sensititre; Trek Diagnostic Systems, Cleveland, OH, USA). The following antimicrobial agents were tested: CXA-101; CXA-101 with a fixed tazobactam concentration of 4 mg/L; CXA-101 with a fixed tazobactam concentration of 8 mg/L; ceftazidime; ceftazidime with a fixed tazobactam concentration of 4 mg/L; ceftazidime with a fixed clavulanate concentration of 4 mg/L; piperacillin; piperacillin with a fixed tazobactam concentration of 4 mg/L; ceftazidime; and imipenem. European Committee on Antimicrobial Susceptibility Testing (EUCAST) breakpoints were used for piperacillin with and without tazobactam, ceftazidime, cefepime and imipenem.7 For CXA-101 with and without tazobactam and for ceftazidime with tazobactam or clavulanate, ceftazidime breakpoints were used tentatively due to the similarities in pharmacokinetic properties.3

Whereas all except one isolate (TEM-4) were resistant to ceftazidime, four isolates (producing SHV-2a, SHV-5, TEM-4 and BEL-1) had CXA-101 MICs of ≤4 mg/L (Table 1). Only one of these isolates was susceptible to piperacillin/tazobactam (producing TEM-4) and one isolate to cefepime (producing BEL-1) when EUCAST breakpoints were applied (for piperacillin/ tazobactam: susceptible, ≤16 mg/L; and resistant, >16 mg/L). In one of these isolates (producing SHV-5) the MIC of

Table 1. MICs (mg/L) of CXA-101 plus tazobactam versus comparators for clinical isolates of P. aeruginosa

<table>
<thead>
<tr>
<th>Strain</th>
<th>β-Lactamase</th>
<th>MIC (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CXA</td>
<td>CXT4</td>
</tr>
<tr>
<td>ATCC 27853</td>
<td>none</td>
<td>0.5</td>
</tr>
<tr>
<td>GW-1</td>
<td>GES-2</td>
<td>&gt;64</td>
</tr>
<tr>
<td>DEJ</td>
<td>GES-9</td>
<td>&gt;64</td>
</tr>
<tr>
<td>15</td>
<td>VEB-1</td>
<td>&gt;64</td>
</tr>
<tr>
<td>RU-1</td>
<td>VEB-1-A</td>
<td>&gt;64</td>
</tr>
<tr>
<td>RN-1</td>
<td>PER-1</td>
<td>&gt;64</td>
</tr>
<tr>
<td>51170</td>
<td>BEL-1</td>
<td>4</td>
</tr>
<tr>
<td>RP1</td>
<td>SHV-2a</td>
<td>4</td>
</tr>
<tr>
<td>1782</td>
<td>SHV-5</td>
<td>4</td>
</tr>
<tr>
<td>SHAM</td>
<td>TEM-4</td>
<td>0.5</td>
</tr>
<tr>
<td>PG13</td>
<td>OXA-32</td>
<td>&gt;64</td>
</tr>
</tbody>
</table>

Abbreviations of antimicrobial agents with susceptibility breakpoints derived from EUCAST in brackets (susceptible ≤/resistant ≥): CXA, CXA-101 (tentative breakpoint 8/8); CXT4, CXA-101 with a fixed tazobactam concentration of 4 mg/L (tentative breakpoint 8/8); CXT8, CXA-101 with a fixed tazobactam concentration of 8 mg/L (tentative breakpoint 8/8); CAZ, ceftazidime (8/8); CAT, ceftazidime with a fixed tazobactam concentration of 4 mg/L (tentative breakpoint 8/8); CAC, ceftazidime with a fixed clavulanate concentration of 2 mg/L (tentative breakpoint 8/8); PIP, piperacillin (16/16); TZP, piperacillin with a fixed tazobactam concentration of 4 mg/L (16/16); FEP, cefepime (8/8); and IPM, imipenem (4/8).
CXA-101 was reduced from 4 to 1 mg/L upon the addition of tazobactam. The addition of tazobactam was of no benefit in strains producing GES, VEB and PER β-lactamases, which all had CXA-101 MICs >64 mg/L. In the only isolate producing an ESBL-M-D β-lactamase (OXA-32), the MIC was reduced from >64 to 8 mg/L. The OXA-32-producing isolate was also susceptible to piperacillin/tazobactam. Susceptibility to piperacillin/tazobactam was additionally seen in one isolate (producing PER-1), which was resistant to all β-lactams except imipenem and ceftazidime plus clavulanate. The latter combination was found to have activity against four isolates (producing PER-1, BEL-1, SHV-5 and TEM-4).

In conclusion, CXA-101 was found to have good in vitro activity against 4/9 ESBL producing P. aeruginosa. The addition of tazobactam extended the activity to the one ESBL-M-D-producing isolate tested. Hence, CXA-101 plus tazobactam had good in vitro activity against half of the ESBL-producing P. aeruginosa isolates investigated. In comparison, imipenem had activity against 9/10 isolates, ceftazidime plus clavulanate against 4/10 isolates, piperacillin/tazobactam against 3/10 isolates, cefepime against 2/10 isolates and ceftazidime or ceftazidime plus tazobactam against 1/10 isolates.

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References

Clinical efficacy of temocillin
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Sir, Livemore and Tulkens1 state that published clinical data on temocillin’s use in severe sepsis and nosocomial pneumonia remain scanty. This is particularly relevant when extended-spectrum β-lactamase (ESBL)-producing Enterobacteriaceae are involved, as therapeutic options are limited.2

Here we present clinical data on the use of temocillin in severe sepsis related to infections of the biliary and urinary tracts, as well as nosocomial pneumonia and diverticulitis. Five patients had infections with Enterobacteriaceae producing ESBLs (three Klebsiella pneumoniae, one Escherichia coli and one dual infection with both K. pneumoniae and E. coli, both ESBL-positive). One patient had ventilator-associated pneumonia (VAP) and bacteraemia: Enterobacter aerogenes (a derepressed mutant with constitutive production of AmpC chromosomal cephalosporinase) and ESBL-negative K. pneumoniae were isolated from sputum, and a fully susceptible Proteus mirabilis from blood (Table 1). Isolates were identified using Phoenix Automated Microbiology System (BD Diagnostic Systems, Sparks, MD, USA) methodology and ESBL/AmpC production was confirmed using Phoenix and/or combination disc methodology. Temocillin MICs were determined by Etest (AB Biodisk, Solna, Sweden).

Infection completely resolved on temocillin in all but two cases, patients 4 and 5. Patient 4 developed a diverticular abscess that was drained radiologically 2 months later, and K. pneumoniae, E. coli (both ESBL-positive), Enterococcus faecium and yeasts were cultured from pus. She was initially treated with meropenem [1 g intravenously (iv) once daily] for 10 days, followed by de-escalation to temocillin (1 g iv thrice weekly with dialysis) and metronidazole (400 mg orally once daily). Definitive surgery was not possible owing to co-morbidities, and temporary withdrawal of temocillin had previously resulted in septic deterioration. She is currently stable on temocillin (1 g iv thrice weekly) and metronidazole (400 mg orally once daily) with a long-term drain in situ.

Patient 5 presented with acute cholangitis on a background of primary biliary cirrhosis, for which she was awaiting liver transplantation. Blood cultures from admission grew an ESBL-producing K. pneumoniae. Inducible AmpC was not detected on induction testing. The isolate was susceptible to...