P0333
Paper Poster Session
Susceptibility trends for old and new antibiotics

Beta-lactamase characterization of baseline Enterobacteriaceae from phase 3 trials of ceftazidime-avibactam (CAZ-AVI) for the treatment of complicated urinary tract infections (cUTIs)

Rodrigo E. Mendes*[1], Mariana Castanheira[1], Leah N. Woosley[1], Gregory Stone[2], Patricia Bradford[3], Robert Flamm[1], Ronald N. Jones[4]

[1]*Jmi Laboratories, North Liberty, United States*

[2]*Astrazeneca, Waltham, MA, United States*

[3]*Astrazeneca Pharmaceuticals, Waltham, Massachusetts, United States*

[4]*Jmi Laboratories, North Liberty, Ia, United States*

Background: CAZ-AVI received U.S. Food and Drug Administration approval for treatment of cUTI, including pyelonephritis, and complicated intra-abdominal infections (in combination with metronidazole) in adult patients with limited or no alternative treatment options. This study characterized the β-lactamase content of Enterobacteriaceae recovered from patients with cUTI in two identical, randomized, multicenter RECAPTURE 1 and 2 Phase 3 trials of CAZ-AVI (D4280C00002; D4280C00004).

Methods: A total of 1,033 patients were enrolled in both trials combined. Susceptibility testing was centrally performed by standard CLSI methods. MIC criteria were pre-established for selecting Enterobacteriaceae for screening of extended-spectrum β-lactamase (ESBL), class C β-lactamase (plasmid AmpC; pAmpC), and/or carbapenemase genes. Isolates underwent microarray-based assay, complemented by PCR/sequencing. Relative transcription of chromosomal AmpC (cAmpC) levels were assessed.

Results: A total of 91 Enterobacteriaceae isolates recovered from 90 subjects at the baseline visit met the MIC screening criteria. One patient had a polymicrobial cUTI caused by *E. coli* and *P. mirabilis. E. coli* isolates were most prevalent (42/91; 46.2%), followed by *Enterobacter* spp. (15/91; 16.5%), *K. pneumoniae* (13/91; 14.3%) and *P. mirabilis* (12/91; 13.2%). A total of 17 (18.7%) and 36 (39.6%) isolates were susceptible to CAZ using EUCAST and CLSI breakpoints, respectively. CAZ-AVI inhibited growth of all but two strains at ≤4 mg/L (89/91; 97.8% susceptible at ≤8 mg/L). Isolates with higher CAZ-AVI MICs were one NDM-1-producing *K. pneumoniae* and one *P. rettgeri* with none of the screened β-lactamases (MIC, 32/4 mg/L for both isolates). Doripenem inhibited 97.9% (89/91) of isolates at the breakpoint for susceptibility (i.e. ≤1 mg/L). A total of 32 (76.2%) *E. coli* harbored $bla_{CTX\text{-}M}$. The other isolates had SHV-2 (1 isolate) SHV-12 (1), SHV-12/CMY-2 (1), KLUC-2 (1), pAmpC (4) and screened β-lactamases were not detected in two *E. coli*. Among *Klebsiella* spp., 9 (60.0%) and 2 (13.3%) isolates produced CTX-M and SHV-2, respectively. Also, three isolates produced NDM-1 (Ukraine), OXA-48 (Romania) or OXA-9 (Romania), whereas none of the β-lactamase genes screened were detected in one *Klebsiella* spp. The majority of *Enterobacter* spp. (12/15; 80.0%) showed overexpression of cAmpC alone or in combination with CTX-M and SHV-12, whereas the remaining isolates produced CTX-M (3/15; 20.0%) alone or in combination with DHA-1 or SHV-12. *P. mirabilis* produced pAmpC (7/12; 58.3%), CTX-M (4/12; 33.3%) or TEM-93 (1/12; 8.3%). *Citrobacter* spp., *Providencia* spp. and *S. marcescens* had overexpression of cAmpC (3/7; 42.9%), CTX-M (2/7; 28.6%), PER-1 (1/7; 14.3%) and one isolates had CTX-M as well as overexpression of cAmpC (1/7; 14.3%).

Conclusions: CAZ-AVI demonstrated potent *in vitro* activity against these β-lactamase-producing organisms causing cUTI in phase 3 clinical trials. CTX-M enzymes prevailed among *E. coli* and

Klebsiella spp. organisms, whereas pAmpC was most common among *P. mirabilis.* Other organisms often overexpressed cAmpC.