Antimicrobial Activity of Ceftazidime Avibactam (formerly NXL104) Tested Against Gram-Negative Organisms Causing Infections in Medical Centers from Europe, Latin America and the Asia-Pacific Region

C2-1251

Background: Carbapenem (IMX-NS) is a novel non-β-lactam β-lactamase inhibitor (BLI), which inhibits Ambler A, C, D, and some D-type β-lactamases. Inactivating these enzymes is important for the treatment of hospital infections, including those caused by antiresistant hospital-acquired Gram-negative (HAGN) bacteria.

Methods: C2-1251 and various comparators were tested by CLSI broth microdilution and Etest methods against 3,333 clinical isolates from medical centers located in Europe (95), South America (40), and APAC region (40) (Tables 1 and 2). The collection included E. coli (32.4/39.3%), P. aeruginosa (28.6/32.9%), K. pneumoniae (18.6/16.1%), and 4.0% non-susceptible (NS). Enterobacter spp. (19.3/24.3%), Citrobacter spp. (10.6/10.6%), S. marcescens (9.5/6.2), and E. coli (0.4%) were excluded. The test results are shown in Tables 1 and 2.

Results: E. coli was the most resistant to meropenem-NS (40), followed by K. pneumoniae. Inactivation of E. coli and K. pneumoniae were achieved by avibactam, with low IC 90%(33.8/39.3%), followed by LA (26.6/37.0%) and EU (24.3/34.2%), while S. marcescens were 80.4/19.6% and S. aureus were 95.6/0.3%. Avibactam protected E. coli against hospital infections, including those caused by resistant hospital-acquired Gram-negative (HAGN) bacteria.

Conclusions: CA2104 was very active against HAGN, including E. coli, KPC, and AmpC producers. In the future, CA2104 will be a useful option for treatment of infections caused by multiple-RGN bacteria.

Introduction

Gram-negative bacteria resistant to currently approved agents present a challenge to the successful treatment of various infections. β-lactamase-mediated resistance in particular, represents a major threat to the effectiveness of β-lactam antibiotics. An approach to resolve the utility of a β-lactam compound is to combine it with novel agents that block β-lactamases, thereby allowing this class to reach resistant concentrations.

Avibactam (avb), a non-β-lactam β-lactamase inhibitor with activity against class A, C, and some D β-lactamases, is inactivated very efficiently by avibactam, with low IC 90%(33.8/39.3%), followed by LA (26.6/37.0%) and EU (24.3/34.2%), while S. marcescens were 80.4/19.6% and S. aureus were 95.6/0.3%. Avibactam protected E. coli against hospital infections, including those caused by resistant hospital-acquired Gram-negative (HAGN) bacteria.

Avibactam combined with ceftazidime (ceftazidime avibactam) is currently undergoing clinical development for severe infections, including bacteraemia and Gram-negative bacillae, cystic fibrosis and intra-abdominal infections (including hospital infections and resistant infections, in each case, treating those caused by multidrug-resistant Gram-negative bacteria). In this study, we evaluated the activity of ceftazidime avibactam against a contemporary collection (2011) of Gram-negative bacteria, including multidrug-resistant, antibiotic-resistant strains from the medical centers in Europe (95), South America (40), and the Asia-Pacific region (40).

Materials and methods

Bacterial isolates: A total of 3,333 non-duplicate, consecutive Gram-negative strains were collected during 2010 from 30 medical centers located in the EU (142 isolates), South America (1003), and APAC region (50) (Table 1). These isolates were collected by local laboratories, according to the guidelines and standards that are currently in use for in vitro antimicrobial susceptibility testing. The collection isolates were stored and subcultured in bile salts-horse serum broth (Oxoid, Basingstoke, Hampshire, UK) and frozen at -70°C. The collection includes Gram-negative bacteria from medical centers located in EU (95), South America (40), and APAC region (40). All 934 isolates were tested using either the CLSI or EUCAST susceptible breakpoint (Tables 1 and 2).

Sensitivity testing: Sensitivity testing was performed by a reference broth microdilution method (CLSI or EUCAST, 2009). Enterobacter species (E. coli and K. pneumoniae), P. aeruginosa, and S. marcescens were excluded for quality control and quality assurance purposes. E. coli and K. pneumoniae were selected for the MIC results of ceftazidime, ceftazidime avibactam, or ampicillin were considered to be phenotypic for ceftazidime avibactam (CLSI, 2011).

Results

• All 90.0% and 75.0% of the meropenem-non-susceptible isolates were susceptible to ceftazidime avibactam with the CLSI and EUCAST susceptible breakpoint for isolates from APAC.

• For E. coli with the CLSI phenotype, ceftazidime avibactam and meropenem are the most potent compounds and provided the broadest coverage (108.0%), followed by the CLSI and EUCAST susceptible breakpoint for isolates from APAC (Tables 3 and 4).

• The MICs of resistance, (MIC-R), were categorized as susceptible to ceftazidime avibactam with the CLSI susceptible breakpoint for ceftazidime and 0.25-16 µg/ml for susceptible isolates. Ceftazidime avibactam showed the highest susceptibility rate followed by meropenem and ceftazidime.

• A total of 60.5% and 75.0% of the non-susceptible isolates were susceptible to ceftazidime avibactam with the CLSI and EUCAST susceptible breakpoint for isolates from APAC.

• The presence of carbapenemases was evaluated by polymerase chain reaction (PCR) analysis using the npx1,IMP, and DDE enzymes. All tested carbapenemases MIC values ≤4.0 µg/ml, six Klebsiella spp., one Enterobacter spp., and one Citrobacter spp. were excluded. Two isolates contained a VIM-like metallo-β-lactamase. One isolate contained class B1 carbapenemase (isolate that contained the carbapenemase KPC-3), which included the S. marcescens E. coli, and S. aureus were susceptible to avibactam, amikacin, ticarcillin-clavulanate, and meropenem.

Conclusions

• The CLSI phenotype isolates among E. coli and Klebsiella were non-susceptible against ceftazidime avibactam, with the EUCAST phenotype, results presented across all regions and most presented in the APAC region.

• Ceftazidime avibactam was very active against these resistant Enterobacteraceae, including E. coli, KPC, and AmpC producers, and the ampicillin MIC range for the isolates was ≤16 µg/ml.

• Ceftazidime avibactam provided the highest overall susceptibility when tested against this contemporary collection of Gram-negative bacteria that were resistant to Meropenem-NS, in particular, in the APAC region.

• The use of avibactam, a broad-spectrum non-β-lactam S. lactococcus lactis, inhibits in combination with the well-known β-lactam antibiotics, may offer a novel pharmacological alternative for treatment of multidrug-resistant Gram-negative bacterial infections.

Selected references


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HS Sader, DJ Farrell, RK Flamm, JM Bell, JD Turnidge, RN Jones

1 JMI Laboratories, North Liberty, IA, USA; South Australia Pathology, Women's & Children's Hospital, Adelaide, Australia

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