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Activity of imipenem/relebactam against *Pseudomonas aeruginosa* with antimicrobial-resistant phenotypes from seven global regions: SMART 2015–2016

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ABSTRACT

Objectives: Relebactam inhibits Ambler class A and C β-lactamases. Imipenem/relebactam has completed one phase 3 clinical study of patients infected with imipenem-non-susceptible Gram-negative bacilli. Two more phase 3 clinical studies are in progress for the treatment of patients with hospital-acquired and ventilator-associated bacterial pneumonia, complicated intra-abdominal infections and complicated urinary tract infections. In the current study, clinical *Pseudomonas aeruginosa* isolates cultured by medical centre laboratories in seven geographic regions (Africa, Asia, Europe, Latin America, Middle East, USA/Canada, South Pacific) were tested for susceptibility to imipenem/relebactam and comparators.
Methods: A total of 12 170 isolates collected as part of the 2015–2016 Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program were tested using the Clinical and Laboratory Standards Institute (CLSI)-defined broth microdilution method. Relebactam was tested at a fixed concentration of 4 μg/mL in combination with doubling dilutions of imipenem. Imipenem/relebactam MICs were interpreted using current CLSI breakpoints for imipenem.
Results: At the imipenem susceptible breakpoint (≤2 μg/mL), imipenem/relebactam inhibited 90.8% of all *P. aeruginosa* isolates and 70.7% of multidrug-resistant (MDR) isolates ($n = 3708$). Relebactam restored imipenem susceptibility to 70.3% (2656/3776) of imipenem-non-susceptible isolates and increased percent susceptibility to imipenem against isolates with ceftazidime-non-susceptible (by 35.2%), piperacillin/tazobactam-non-susceptible (by 36.6%), cefepime-non-susceptible (by 36.8%) and MDR (by 41.9%) phenotypes. Across the seven geographic regions studied, susceptibility to imipenem/relebactam ranged from 84.0% (Latin America) to 96.0% (South Pacific).
Conclusions: Imipenem/relebactam could provide an important treatment option against infections with *P. aeruginosa* isolates that are non-susceptible to several currently available antipseudomonal β-lactams.

1. Introduction

Pseudomonas aeruginosa is an opportunistic human pathogen frequently related to water exposure, aerosol inhalation and biofilm formation. It is most often identified as an aetiological agent in critically ill or immunosuppressed patients with hospital-associated bloodstream, respiratory tract, urinary tract or wound infections [1,2]. *Pseudomonas aeruginosa* is one of the 'ESKAPE' pathogens (*Enterococcus faecium*, *Staphylococcus aureus*, *Klebsiella pneumoniae*, *Acinetobacter baumannii*, *P. aeruginosa* and *Enterobacter* spp.) known to be responsible for a majority of antimicrobial-resistant hospital-associated infections [3]. Treatment of pseudomonal infections has been made increasingly complex by the emergence of, and increase in, multidrug-resistant (MDR) phenotypes that restrict, or sometimes obviate, all potentially effective antimicrobial agents [1,4,5]. Carbapenems and antipseudomonal cephalosporins are critical components of therapeutic regimens for patients with serious pseudomonal infections [6]. However, resistance to carbapenems and antipseudomonal β-lactams is a component of many MDR phenotypes [6,7]. Clinical *P.*

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aeruginosa isolates with MDR phenotypes are associated with delays in appropriate antimicrobial therapy, adverse clinical outcomes, and the risk of therapeutic agent-related adverse effects if amikacin or colistin is added to a patient's treatment regimen [5,8,9]. New antimicrobial agents capable of treating patients with MDR *P. aeruginosa* infections are urgently required [10,11].

One approach to overcoming resistance to carbapenems and extended-spectrum cephalosporins in Gram-negative bacilli rests with the development of improved β-lactamase inhibitors to use in combination with current β-lactams. Relebactam (formerly MK-7655) is a diazabicyclooctane, non-β-lactam β-lactamase inhibitor of Ambler class A, including KPC-type carbapenemases, and class C β-lactamases [12]. Relebactam does not inhibit Ambler class B or D β-lactamases. Relebactam is in development in combination with the carbapenem/renal dehydropeptidase I inhibitor, imipenem/cilastatin, to restore the inhibitory activity of imipenem against KPC-producing *K. pneumoniae*, other carbapenem-resistant Enterobacteriaceae and carbapenem-resistant *P. aeruginosa*. Neither imipenem nor relebactam are subject to efflux by *P. aeruginosa*, making them excellent partner agents to treat pseudomonal infections [13]. Imipenem/relebactam has completed one phase 3 clinical study of patients infected with imipenem-non-susceptible Gram-negative bacilli. Two more phase 3 clinical studies are in progress for the treatment of patients with hospital-acquired and ventilator-associated bacterial pneumonia, complicated intra-abdominal infections and complicated urinary tract infections [14].

The current study evaluated the in vitro activity of imipenem/relebactam, imipenem and comparator antipseudomonal agents against a current (2015–2016) collection of clinical *P. aeruginosa* isolates from seven global regions, including β-lactam-non-susceptible and MDR subsets. Isolates tested in this study were collected as part of the 2015–2016 Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program, which has monitored the in vitro antimicrobial susceptibility profiles of clinical isolates of aerobic and facultative Gram-negative bacilli collected by laboratories worldwide from intra-abdominal (since 2002), urinary tract (since 2009) and lower respiratory tract (since 2015) patient specimens [15].

2. Materials and methods

2.1. Clinical isolates

The SMART global surveillance program requests participating medical centre laboratories to annually collect consecutive aerobic and/or facultative Gram-negative pathogens cultured from lower respiratory tract ($n = 100$), intra-abdominal ($n = 100$) or urinary tract ($n = 50$) specimens of unique patients. Isolates are transported to International Health Management Associates, Inc. (IHMA, Schaumburg, IL) or IHMA Europe Sàrl (Monthey, Switzerland), which serve as the co-ordinating laboratories. Participating medical centre laboratories in China and India followed a different process; isolates collected in China were sent to Peking Union Medical College Hospital (Beijing, China) and isolates collected in India were sent to Christian Medical College (Vellore, India) for confirmatory identification and antimicrobial susceptibility testing. Data from the testing laboratories in China and India were then transferred to IHMA for review and inclusion in the SMART global surveillance program data set.

In 2015 and 2016, the SMART global surveillance program collected 12 170 *P. aeruginosa* isolates from 190 hospitals in 53 countries across seven global regions (Supplementary Table S1). The number of isolates of *P. aeruginosa* confirmed and tested from each global region (number of countries; number of participating medical centre laboratories) were: 3338 isolates from Europe (17 countries; 49 laboratories); 2623 isolates from Asia (10 countries, 49 laboratories); 2330 isolates from USA/Canada (2 countries, 29 laboratories); 1452 isolates from Latin America (11 countries, 29 laboratories); 903 isolates from South Pacific (3 countries, 11 laboratories); 773 isolates from Africa (4 countries, 11 laboratories); and 751 isolates from the Middle East (6 countries, 12 laboratories). The identity of each isolate received by the SMART global surveillance program was confirmed as *P. aeruginosa* using matrix-assisted laser desorption/ionisation time-of-flight mass spectrometry (MALDI-TOF/MS) (Biotyper instrument; Bruker Daltonics, Billerica, MA).

2.2. Antimicrobial susceptibility testing

Antimicrobial susceptibility testing was performed according to the Clinical and Laboratory Standards Institute (CLSI) reference broth microdilution standard method [16,17] using custom-made dehydrated Trek Diagnostic Systems 96-well panels (Thermo Scientific, Independence, OH). Relebactam was tested at a fixed concentration of 4 μg/mL in combination with doubling dilutions of imipenem [16]. Minimum inhibitory concentrations (MICs) were interpreted by applying current CLSI breakpoints for all agents tested except imipenem/relebactam for which no breakpoints exist. For comparison purposes, current CLSI MIC breakpoints for imipenem tested against *P. aeruginosa* were used for imipenem/relebactam (≤2 μg/mL, susceptible; 4 μg/mL, intermediate; ≥8 μg/mL, resistant) [16]. Multidrug resistance was defined as non-susceptibility (i.e. intermediate or resistant) to any three or more of the following eight sentinel antimicrobial agents: amikacin; aztreonam; cefepime; ceftazidime; ciprofloxacin; colistin; imipenem; and piperacillin/tazobactam (TZP).

3. Results

The SMART global surveillance program collected 77 405 isolates of Gram-negative bacilli across seven global regions (Africa, Asia, Europe, Latin America, Middle East, USA/Canada and South Pacific) in 2015 and 2016 (Supplementary Table S2). *Pseudomonas aeruginosa* accounted for 15.7% (12 170/77 405) of all Gram-negative bacilli collected; across the seven global regions, the percentage of isolates of Gram-negative bacilli that were *P. aeruginosa* ranged from 13.0% in Latin America to 19.5% in USA/Canada. The 12 170 isolates of *P. aeruginosa* were predominantly from respiratory tract specimens (64.8%; 7888/12 170), with 23.7% (2884/12 170), 10.8% (1320/12 170) and 0.6% (78/12 170) from intra-abdominal, urinary tract and unknown specimen types, respectively (Supplementary Table S3). *Pseudomonas aeruginosa* were isolated predominantly from specimens of patients aged 18–64 years (46.6%; 5675/12 170) and ≥65 years (45.3%; 5516/12 170) (Supplementary Table S4).

Table 1 summarises the activities of imipenem/relebactam, imipenem and eight comparator agents tested against all isolates of *P. aeruginosa* collected in 2015–2016 as well as against subsets of isolates with specific β-lactam-non-susceptible and MDR phenotypes. Overall, against all isolates of *P. aeruginosa*, colistin demonstrated the highest rate of susceptibility of all agents tested (99.0% susceptible), followed by amikacin (91.1% susceptible) and imipenem/relebactam (90.8% susceptible at the imipenem susceptible breakpoint of ≤2 μg/mL) [16]. Percent susceptibilities to the remaining seven agents ranged between 64.8% (aztreonam) and 75.0% (cefepime). Susceptibility rates to the tested cephalosporins, aztreonam, fluoroquinolones, TZP and imipenem were typically between ca. 15% and 25% lower than for imipenem/relebactam for all isolates of *P. aeruginosa* and between ca. 25% and 60% lower than for imipenem/relebactam for isolate subsets containing β-lactam-non-susceptible and MDR phenotypes.