Activity of Sulbactam-Durlobactam and Comparators Against a National Collection of Carbapenem-Resistant Acinetobacter baumannii Isolates From Greece

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Background: Acinetobacter baumannii is a leading cause of healthcare-associated infections worldwide, due to both its persistence in the hospital setting and ability to acquire high levels of antibiotic resistance. Carbapenem-resistant A. baumannii isolates (CRAB) limit the activity of current antimicrobial regimens and new alternatives or adjuncts to traditional antibiotics are urgently needed. Durlobactam is a novel broad-spectrum inhibitor of serine-type β-lactamases that restores sulbactam (SUL) activity against A. baumannii. The sulbactam-durlobactam (SD) combination has recently completed Phase 3 testing in the global ATTACK trial.

Objectives: The aim of this study is to evaluate the in vitro activity of SD versus comparators against a representative nationwide collection of CRAB isolates.

Methods: One hundred ninety CRAB isolates were collected from clinical samples of patients hospitalized in 11 hospitals throughout Greece during 2015. In vitro activities of SD and comparators (SUL alone, amikacin, minocycline, imipenem, meropenem, colistin, SD and imipenem combined with SD) were determined by broth microdilution.

Results: Durlobactam restored sulbactam activity against the majority of the strains tested, with SD exhibiting the lowest MIC90 (8 µg/ml) relative to the other single comparators tested; 87.9% of the isolates had SD MICs ≤4/4 µg/ml. The most active comparator was colistin (MIC90 = 16 µg/ml). The addition of imipenem further lowered the MIC90 of SD by one two-fold dilution.

Conclusions: This study demonstrated the potential utility of SD for the treatment of infections caused by A. baumannii. If its clinical efficacy is confirmed, SD may be an important therapeutic option for CRAB infections.

Keywords: hospital infections, diazabicyclooctane, durlobactam, carbapenemases, beta-lactamase inhibitor, serine-type beta-lactamases, CRAB infections, sulbactam-durlobactam-imipenem
INTRODUCTION

Infections caused by multidrug-resistant (MDR) A. baumannii pose a serious threat to global health. These infections include ventilator-associated pneumonia, bacteremia, complicated urinary tract infections and skin and soft tissue infections, in both healthy and immuno-compromised individuals (Lee et al., 2017). The mortality rates of these infections reach 33%, and carbapenem resistance (Seifert et al., 2020; Shapiro et al., 2021). SUL inhibits class D β-lactamases, such as PBP1a, PBP1b and PBP3 (Higgins et al., 2014). However, due to the presence of β-lactamases that are involved in bacterial peptidoglycan synthesis, such as PBP1a, PBP1b and PBP3, SUL has limited activity against class A serine β-lactamase inhibitors, with limited activity against class A serine β-lactamases (Seifert et al., 2020; Shapiro et al., 2021) as well as diverse clinical isolates, in international, contemporaneous surveillance studies (McLeod et al., 2020; Yang et al., 2020; Nodari et al. 2021). SD is currently in late-stage development for use in the treatment of infections caused by Acinetobacter spp.

The aim of this study was to examine the in vitro potency of the SD combination on a collection of previously characterized, non-duplicate isolates of CRAB from Greece harboring acquired β-lactamases.

MATERIALS AND METHODS

Bacterial Strains

The study included 190 non-repetitive CRAB isolates recovered during 2015 from 11 geographically distinct tertiary hospitals, located throughout Greece and selected during a previous nationwide study randomly from a collection of 2,500 A. baumannii isolates. The clinical samples included blood, bronchial aspirates, urine, superficial or deep tissue wounds, peritoneal and pleural effusions, cerebrospinal fluids and intra-abdominal secretions. All isolates were previously characterized and confirmed to be A. baumannii by PCR/sequencing for the intrinsic blaOXA-51-like gene (Pournaras et al., 2017). In particular, clonality was tested by a scheme based on two multiplex PCRs, that selectively amplified alleles of the ampC, cscE and blaOXA-51-like (Turton et al., 2007; Giannouli et al., 2010) and single-locus blaOXA-51-like sequence-based typing (SBT) (Pournaras et al., 2014). The SBT assigned 153 isolates (80.5%) to IC2, 36 isolates to IC1 (18.9%) and 1 isolate to G6 (0.5%). Of the 153 IC2 isolates, all had blaOXA-23-like and three had both blaOXA-23-like and blaOXA-58-like. As far as IC1 clone, 34 isolates (94.5%) had blaOXA-23-like and two (5.5%) had blaOXA-58-like. As for the β-lactamases carried by the study isolates, the blaOXA-23-like gene was identified in 187 isolates (98.4%), blaOXA-23-like together with blaOXA-58-like in three (1.6%), blaOXA-58-like in two (1.0%) and blaOXA-40-like in one isolate (0.5%).

Antimicrobial Susceptibility

Antimicrobial susceptibility was determined using broth microdilution in freshly prepared cation-adjusted Mueller–Hinton broth (CAMHB) following CLSI recommendations (CLSI, 2018; CLSI, 2019). Pre-manufactured, frozen 96-well plates containing 50 µl of 2x antimicrobial drug concentrations were supplied by Entasis Therapeutics. The 190 CRAB isolates were tested against SUL, amikacin (AMK), minocycline (MIN), imipenem (IMP), meropenem (MER), colistin (COL), SD and IMP combined with SD (SID). The concentration ranges tested in 2-fold dilutions were for SUL, 0.06 to 64 µg/ml; SD [durlobactam (DUR) fixed at 4 µg/ml], 0.06/4 to 64/4 µg/ml; SID (1/1/2 ratio), 0.06/0.06/0.12 to 64/64/128; AMK, 0.12 to 128 µg/ml; COL, 0.06 to 64 µg/ml; IMP, 0.06 to 64 µg/ml; MER, 0.06 to 64 µg/ml; and MIN, 0.03 to 32 µg/ml. The combination of SUL, IMP and DUR was tested in a fixed 1:1:2 ratio titrated in 2-fold dilutions. MICs were interpreted according to CLSI guidelines and susceptibilities were determined using CLSI breakpoints, where applicable. Each experiment included testing of CLSI-approved quality control organisms NCTC 13304 (A. baumannii), ATCC 25922 (Escherichia coli) and ATCC 27853 (Pseudomonas aeruginosa). The minimal inhibitory concentration (MIC) of each antibiotic was determined by visual inspection for each strain after incubation for 20 hours at 35°C.

Next Generation Sequencing of Isolates With Elevated SD MICs

Three isolates with SD MICs >8/4 µg/ml were analyzed by Next Generation Sequencing. Genomic DNA was purified from the isolates using a Sigma-Aldrich GenElute bacterial genomic DNA kit. Genomic libraries were assembled using a Nextera XT library preparation kit and sequenced using an Illumina MiSeq system with 300-bp paired-end reads and a coverage of ≥ 50X. Assembly
and analysis of the whole genome sequencing was performed using CLC Genomics Workbench v21.0.3 (Qiagen, Germantown, MD). Paired Fastq files were processed and analyzed as follows: raw reads were trimmed of any remaining barcode sequences as well as trimmed for quality. Reads were then de novo assembled using fraction length=0.8 and similarity fraction=0.9 using default mismatch/insertion/deletion costs. Consensus sequences were extracted and contigs greater than 500bp were assembled. B-lactamase genes for each strain were identified using BLAST against a local β-lactamase database. Additionally, mutations in efflux, permeation, and PBP proteins were identified by BLAST analysis against the A. baumannii ATCC 17978 reference strain. The genomic sequences of the three strains tested were deposited at http://www.ncbi.nlm.nih.gov/bioproject/781741.

RESULTS

The SD MIC50/90 values were 4/4 and 8/4 µg/ml, respectively. The SID MIC50/90 values were 2/2/4 and 8/4 µg/ml, respectively (Table 1). The MIC50/90 values of currently-used comparator antimicrobials were: SUL (64/64), COL (2/16), MIN (16/32), IMP (>64/64), MER (>64/64), and AMK (>128/128) µg/ml (Table 2).

All isolates had IMP and MER MICs ≥32 µg/ml. Resistance rates to comparators were as follows: IMP, 100%; MER, 100%; AMK, 97.4%; and MIN, 57.3%. Of concern, 61 of the 190 (32.1%) isolates were resistant to COL and among isolates from blood cultures, the resistance rate reached 36%. Among the COL-resistant isolates, 54 (88.5%) had low SD MICs of ≤4 µg/ml and all (100%) had SID MICs of ≤4/4/8 µg/ml.

Of the isolates, 87.9% had SD MICs of ≤4/4 µg/ml and only three isolates had SD MIC >8 µg/ml. These three isolates were submitted to NGS sequencing. The genomic characteristics of these isolates are shown in Table 3. In brief, they belonged to three different MLST types (ST-1834, SD MIC 16 µg/ml; ST-1294 SD MIC >64 µg/ml; and ST-425, SD MIC 16 µg/ml). They all carried blaOXA-23 and blaOXA-66 and all encoded the same A515V variant of the PBP3 gene that likely confers resistance to SUL, considering its proximity to the SUL binding site (Papp-Walace et al., 2012). The SID MIC for both ST-1834 and ST-425 isolates was 4 µg/ml (i.e., addition of IMP helped reduce the SD MIC), while the ST-1294 isolate had SD MIC of >64 µg/ml and SID MIC 64/64/128 µg/ml. The latter isolate also harbored the NDM metallo-β-lactamase gene, which DUR does not inhibit.

**DISCUSSION**

The most prevalent mechanism of carbapenem resistance among A. baumannii is associated with carbapenem-hydrolysing enzymes that belong to Ambler class D and B β-lactamases (Jeon et al., 2015; Lee et al., 2017; Wong et al., 2017; Lötsch et al., 2020). The rapid rise of carbapenem resistance among A. baumannii isolates limits the available therapeutic options and poses a serious need for new antimicrobial agents. In particular, according to 2019 data from the European Antimicrobial Resistance Surveillance Network (EARS-Net), nearly a third of invasive Acinetobacter spp. isolates in the EU/EEA are already resistant to carbapenems [European Centre for Disease Prevention and Control (ECDC), 2019; Lötsch et al., 2020]. Carbapenem resistance rates are higher than 50% in southern and eastern European countries [European Centre for Disease Prevention and Control (ECDC), 2019], while in Greece, according to data from the Hellenic CDC, IMP resistance rates are currently exceeding 90% (WHONET). Of note, in our representative countrywide collection, CRAB isolates exhibited particularly high levels of resistance to last-line antimicrobials in addition to carbapenems, including AMK, SUL, MIN and COL.

Among the few therapeutic options that show efficacy against CRAB isolates is COL, used both as monotherapy or in combination with other antimicrobials. Still, while COL is a key drug, there are concerns, not only about its toxicity profiles, but also its rising resistance rates (Viehman et al., 2014). A meta-analysis on the prevalence of A. baumannii antimicrobial resistance worldwide from 2000 to 2017, showed that the overall global resistance rate reaches 11.2% (Pormohammad et al., 2020). Herein, COL showed a much higher resistance rate of 32.1% and among isolates, collected from blood cultures, the rate reached 36%.

The carbapenem resistance problem of A. baumannii can be overcome by the use of expanded-spectrum serine β-lactamase inhibitors, which may inhibit class A, C or D β-lactamases, resulting in restoration of β-lactam activity. SD is a promising combination and its spectrum of activity can address MDR A. baumannii. In our study, the addition of DUR at a fixed concentration of 4 µg/ml lowered the MIC50 and MIC90 of SUL from 64 and >64 to 4 and 8 µg/ml, respectively, except for the isolate that encoded metallo-β-lactamase. The MIC90 of SD was considerably lower than the MIC90 of carbapenems, MIN and AMK and also lower from that of COL [16 µg/ml]. 88.5% of non-susceptible to COL isolates had SD MICs ≤4 µg/ml.

A. baumannii isolates belonging to ICI showed generally more sensitive profiles compared to IC2, concerning SUL, COL.

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**TABLE 1** | MIC distribution of the 190 CRAB isolates for SUL, SD and SID and their MIC50, MIC90 values.

| Antimicrobial agent | SUL | SD | SID (1:1:2) |
|--------------------|-----|----|------------|
|                    | 0.5 | 1  | 2  | 4  | 8  | 16 | 32 | >64 | MIC50 | MIC90 |
| SUL                | 2   | 20 | 61 | 84 | 8  | 11 | 82 | 77 | 17  | 64   | >64  |
| (Durlobactam fixed |     |    |    |    |    |    |    |    |     |      |      |
| at 4 µg/ml)       | 2   | 19 | 84 | 83 | 1  | 1  | 2  | 4  |     |      |      |
and carbapenems. For MIN, the resistance rates between IC1 and IC2 isolates were 2.8% and 71.2%, respectively. There was no difference on the MICs of SD and SID among the isolates of the two clonal lineages. For both IC2 and IC2 isolates, MIC50/90 of SD and SID were at 4/4 and 2/4, respectively.

Compared to other studies on the activity of SD, our collection of isolates presented higher resistance rates and MICs for the comparators, as well as for SD. In particular, both the SD MIC50 and MIC90 of the strains in the present study exceeded by one to three-fold the respective values of those reported in international studies (McLeod et al., 2020; Seifert et al., 2020; Yang et al., 2020; Nodari et al., 2021), indicating the presence of less susceptible strains in Greek hospitals. COL MICs were also considerably lower in three of those studies (MIC90 1 mg/ml in references Higgins et al., 2004; Pournaras et al., 2017; Seifert 2020), with only one study from China reporting COL MIC90 128 mg/ml (Durand-Réville et al., 2017). Interestingly, the addition of IMP to SD lowered its MIC90 by one two-fold dilution.

Our study clearly showed that SD had excellent in vitro activity against CRAB isolates that were highly resistant to IMP, MER, AMK, MIN and COL. In addition, SD showed favorable clinical efficacy and safety in a recently completed, global phase 3 study (Entasis Therapeutics, 2019), https://investors.entasistx.com/news-releases/news-release-details/entasis-therapeutics-announces-positive-topline-results). If approved this combination may provide an important therapeutic option for infections due to MDR A. baumannii, including CRAB.

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DATA AVAILABILITY STATEMENT
The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

AUTHOR CONTRIBUTIONS
All authors listed have made a substantial, direct and intellectual contribution to the work, and approved it for publication.

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### TABLE 2 | Resistance rates of the 190 CRAB isolates and their international clonal lineages IC1 and IC2 for SUL, COL, IMP, MER, AMK, MIN, SD and SID and their MIC50, MIC90 values.

| Antimicrobial agent | OVERALL (n = 190) | IC1 (n = 36) | IC2 (n = 153) |
|---------------------|------------------|-------------|-------------|
|                     | MIC50 | MIC90 | % S | % I | % R | MIC50 | MIC90 | % S | % I | % R | MIC50 | MIC90 | % S | % I | % R |
| SUL                 | 64    | >64   | –   | –   | –   | 32    | 64    | –   | –   | –   | 64    | >64   | –   | –   | –   |
| COL                 | 2     | 16    | 67.9 | 0   | 32.1 | 1     | 16    | 75   | 0   | 25  | 2     | 16    | 66   | 0   | 34  |
| IMP                 | >64   | >64   | 0   | 0   | 100  | >64   | >64   | 0   | 0   | 100  | >64   | >64   | 0   | 0   | 100  |
| MER                 | >64   | >64   | 0   | 0   | 100  | >64   | >64   | 0   | 0   | 100  | >64   | >64   | 0   | 0   | 100  |
| AMK                 | >128  | >128  | 2.1 | 0.5 | 97.4 | >128  | >128  | 2.8 | 0   | 97.2 | >128  | >128  | 2   | 0    | 97.3 |
| MIN                 | 16    | 32    | 25.3 | 17.4 | 57.3 | 2     | 4     | 97.2 | 2   | 2.8 | 16    | 32    | 7.8  | 21  | 71.2 |
| SD (Durlobactam fixed at 4 µg/ml) | 4     | 8     | –   | –   | –   | 4     | 4     | –   | –   | –   | 4     | 4     | –   | –   | –   |
| SID (1:1:2)         | 2     | 4     | –   | –   | –   | 2     | 4     | –   | –   | –   | 2     | 4     | –   | –   | –   |

### TABLE 3 | Accession numbers and resistance mechanisms detected by next generation sequencing of the three isolates with SD MICs > 8 µg/ml.

| Genome accession | SD MICs (µg/ml) | SID MICs (µg/ml) | MLST Classification | Encoded BLAs | Other mutations |
|------------------|----------------|-----------------|---------------------|---------------|----------------|
|                  |                 |                 |                     |               |                |
| JAJKGX0000000000 | 16              | 4/4/8           | ST-1834, 436/PST-2  | TEM-1         | –              |
|                  |                 |                 |                     | ADC-73        | OXA-23; OXA-66 |
|                  |                 |                 |                     |               |                |
| JAJGKW0000000000 | >64             | 64/64/128       | ST-1294/PST-570    | TEM-1         | NDM-1          |
|                  |                 |                 |                     | ADC-73        | OXA-23; OXA-66 |
|                  |                 |                 |                     |               |                |
| JAJKGV0000000000 | 16              | 4/4/8           | ST-425/PST-2       | –             | ADC-188        |
|                  |                 |                 |                     |               | OXA-23; OXA-66 |

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