Microbiological Profile

The importance of beta-lactamase inhibitors goes back to early 1970s, when clavulanic acid was discovered, and soon after, sulbactam and tazobactam were added to the therapeutic arsenal. Beta-lactamase inhibitors can restore the activity of beta-lactam antibiotics by inhibiting bacteria beta-lactamases. Recently, at least 2 new groups of inhibitors have appeared: diazobicyclooctanes (DBOs) (as avibactam and relebactam) and boronic acid derivatives (as vaborbactam) [4]. Relebactam is a non-beta-lactam compound formed of a five-membered diazabicyclooctane ring with an amide group. It targets the active-site of serine beta-lactamases via carbamylation. Moreover, the piperidine ring at the 2-position carbonyl group provides a positive charge that prevents its efflux from bacterial cells [4].

Relebactam has no intrinsic antibacterial activity by itself and usually inhibits acquired and intrinsic beta-lactamases. It protects imipenem from degradation by Ambler class A (such as KPCs) and class C (such as AmpC) beta-lactamases and Pseudomonas-derived cephalosporinases. However, relebactam is not active against class B metallo-beta-lactamases or class D oxacillinas. In vitro, relebactam addition decrease the minimum inhibitory concentration (MIC) of imipenem by 2- to 128-fold against extended spectrum beta-lactamase (ESBL) or KPC-producing Enterobacteriales [1].

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From February to May 2013 a multicentre study was performed in 34 Spanish hospitals collecting 245 carbapenemase positive clinical isolates. K. pneumoniae was the specie most frequently isolated (74%) and carbapenemases belong to the following groups: OXA-48 (74%), metallo-beta-lactamase (24%) and KPC (2%) [5]. Data obtained in Hospital Universitario de La Princesa during 2020-2021 showed similar results (Table 1).

IMI/REL susceptibility rates were >90% against seven of the ten most found Enterobacteriales species collected world-
wide as part of the SMART 2017 surveillance program [1]. The susceptibility rates were *Escherichia coli* 99.6%, *K. pneumoniae* 93.0%, *Enterobacter cloacae* 96.8%, *K. oxytoca* 99.4%, *K. aerogenes* 97.6%, *Citrobacter freundii* 98.9% and *C. koseri* 99.8%. IMI/REL demonstrated modest or weak activity against *Serratia marcescens* 70.6%, *Morganella morgani* 32.0% and *Proteus mirabilis* 63.0%. Imipenem shows decreased activity against *Morganella, Proteus* and *Providencia* species due to a mechanism independent of beta-lactamase production so, it is not restored by a beta-lactam inhibitor [1]. IMI/REL also demonstrated potent *in vitro* activity against *P. aeruginosa* isolates [6], Castanheira et al. tested IMI/REL in 45 carbapenemase-negative carbapenem-resistant *Enterobacteriaceae* collected in US hospitals during 3 years with different resistance mechanisms as porin alterations, hyperproduction of efflux system or elevated expression of intrinsic and acquired beta-lactamases and IMI/REL inhibited 88.9% of the strains tested and 93% when *Proteus mirabilis* were not included [7].

To sum up, IMI/REL is active against a wide variety of Gram-negative pathogens, including KPC- and ESBL-producing isolates from different species of *Enterobacteriaceae* and extensively drug-resistant *P. aeruginosa*, both imipenem-resistant strains due to OprD deficiency and GES-1, PER-1 and extended-spectrum OXA enzymes producers [4].

**PHARMACOLOGICAL PROFILE: PHARMACOKINETICS AND PHARMACODYNAMICS**

The pharmacokinetics of imipenem/cilastatin are not affected when coadministered with relebactam. The Cmax and AUC of IMI/REL increase in proportion to dose. The elimination half-lives (t1/2) of IMI/REL are independent of concentration. When imipenem and cilastatin to human plasma proteins is approximately 20% and 40% respectively. The binding of relebactam to human plasma proteins is approximately 22% and is independent of concentration. When imipenem and cilastatin are given concomitantly, adequate levels of imipenem (approximately 70% of the dose) are achieved in the urine enabling antibacterial activity. Cilastatin and relebactam are mainly eliminated in the urine as unchanged parent drugs. IMI/REL is mainly excreted by the kidneys, involving both glomerular filtration and active tubular secretion. The mean terminal elimination half-lives of imipenem/cilastatin and relebactam are 1.0 h and 1.2 h, respectively. Sex, age and weight have no clinically relevant effects on de pharmacokinetics of IMI/REL. The safety and efficacy of IMI/REL in children and adolescents below 18 years of age have not yet been established, no data are available. Hepatic impairment is not likely to have any effect on IMI/REL exposures, as the drugs are primarily cleared renally. No dose adjustment is required in patients with impaired hepatic function. Drug-drug interactions when co-administered with CYP inhibitors or inducers are unlikely. Based on reports of the concomitant use of imipenem/cilastatin, coadministration of IMI/REL with the anticonvulsant valproic acid/divalprox sodium or the antiviral ganciclovir is not recommended. Patients who have a CrCl less than 90 mL/min require dosage reduction. Patients with CrCl less 15 mL/min should not receive IMI/REL unless haemodialysis is instituted within 48 hours. There is inadequate information to recommend the use to patients undergoing peritoneal dialysis [1,8].

**CLINICAL EVIDENCE**

Preclinical studies, phase 1, dose-ranging and pharmacokinetic analysis support imipenem 500 mg/cilastatin 500 mg with 250 mg relebactam every 6 h. This dose showed efficacies in the RESTORE IMI-1 study, a multicenter, randomized, double-blind trial comparing efficacy and safety the IMI/REL vs colistin and imipenem in patients with imipenem non-susceptible bacterial infections, showing that IMI/REL was effective and well-tolerated in this patient profile [9].

The study RESTORE IMI-2 was phase 3, randomized, double-blind, no inferiority trial evaluating IMI/REL vs PIP/TAZ for HAP/VAP. Inclusion criteria were patients ≥18 years old requiring intravenous antibiotics for non-ventilated HAP, ventilated HAP or VAP. A lower respiratory tract sample was collected 48 h before randomization. Exclusion criteria: the previous taking of antibiotics, isolation of only Gram-positive microorganisms in respiratory sample, creatinine clearance <15 mL/min or need for dialysis, suspicion of non-bacterial pneumonia, obstructive pneumonia due to suspicion of cancer, immunodeficiencies, drug interaction and survival <72 h and diseases such as tuberculosis, cystic fibrosis, or endocarditis.

Patients were randomized 1 IMI/REL:1 PIP/TAZ and stratified by ventilated or unventilated HAP/VAP and by Acute Physiology and Chronic Health evaluation II (APACHE II) score <15 vs ≥15. The treatment was 7-14 days, 14 days if pneumonia was associated with detection of *P. aeruginosa* or bacteremia. All patients received empirically linezolid (600 mg/12 h) intravenous, until the existence of methicillin-resistant *S. aureus* (MRSA) was ruled out. If MRSA was present, linezolid was continued ≥7 days or ≥14 days if there was MRSA bacteremia. The visits were developed on day 1 (randomization), 3, 6, 10, EOT (end of therapy), EFU (early flow up) and 28 days. Respiratory samples were collected on EOT and EFU days. Clinical symptoms and signs and adverse effects were monitored daily. Chest X-ray was performed before randomization, EOT, EFU

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**Table 1**  
**Type of carbapenemase detected in carbapenemase producer *Enterobacterales* isolated during 2020 and 2021 in Hospital Universitario de la Princesa.**

| Carbapenemase Type | E. coli | E. cloacae | K. pneumoniae |
|--------------------|---------|------------|---------------|
| KPC                | 2 (1.8%)| 18 (4.4%)  |               |
| OXA-48             | 22 (81.5%)| 71 (65.8%)| 358 (88.4%)   |
| VIM                | 5 (18.5%)| 35 (32.4%)| 29 (7.2%)     |
| Total number included | 27     | 108       | 405           |

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R. Mª Girón, et al.  
New evidence in severe pneumonia: imipenem/cilastatin/relebactam

Rev Esp Quimioter 2022; 35 (Suppl. 1): 46-49
CONCLUSION

Relebactam is a class A and class C beta-lactam inhibitor. IMI/REL was effective in KPCs and P. aeruginosa resistant to carbapenems (non-metallo-carbapenemase) and showed no PIP/TAZ inferiority in HAP and VAP (RESTORE IMI-2 study). IMI/REL is indicated in HAP and VAP in adults, as well as infections due to Gram-negative aerobic organisms in adults with limited treatment options.

CONFLICTS OF INTEREST

Authors declare no conflicts of interest

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