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New antimicrobial alternatives in the treatment of pneumonia

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New evidence in severe pneumonia: imipenem/cilastatin/relebactam

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ABSTRACT

Imipenem combined with beta-lactamase inhibitor relebactam (IMI/REL) has an extensive bactericidal activity against Gram-negative pathogens producing class A or class C beta-lactamases, not active against class B and class D. The phase 3 clinical trial (RESTORE-IMI-2), double-blind, randomized, evaluated IMI/REL vs. piperacillin-tazobactam (PIP/TAZ) for treatment of hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP), demonstrated non-inferiority at all-cause mortality at 28 days (15.9% vs 21.3%), favorable clinical response at 7-14 days end of treatment (61% vs 59.8%) and with minor serious adverse effects (26.7% vs 32%). IMI/REL is a therapeutic option in HAP and VAP at approved dosage imipenem 500 mg, cilastatin 500 mg and relebactam 250 mg once every 6h, by an IV infusion over 30 min.

Key words: Carbapenem resistant; Hospital acquired pneumonia; ventilator-associated bacterial pneumonia, nosocomial pneumonia.

INTRODUCTION

Early selection of the appropriate antibiotic in severe infections significantly reduces mortality. The increased use of carbapenems has led to the development of bacterial strains producing carbapenemases. *Enterobacterales* harboring class A carbapenemase (KPC, *Klebsiella pneumoniae* carbapenemase) constitute a problem within hospital infections. IMI/REL is a new antibiotic combination, bactericidal by its binding inhibition to penicillin binding proteins (PBP1 and PBP2). Recently, it has been approved by the FDA for use in ventilator-associated pneumonia (VAP) and hospital-acquired pneumonia (HAP) in June 2020 [1-3].

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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 the 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 oxacillinases. 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 *Enterobacterales* [1].

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 Enterobacterales species collected world-

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

	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

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 morganii* 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 *Enterobacterales* 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 *Enterobacterales* 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 dose. The binding of 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 enable antibacterial activity. Cilastatin and relebactam are mainly eliminates 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, race, 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].

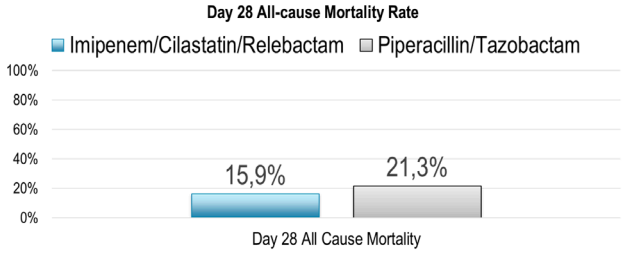
CLINICAL EVIDENCE

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 48h before randomization. Exclusion criteria: the previous taking of antibiotics, isolation of only Gram-positive microorganisms in respiratory sample, creatinine clearance <15mL/min or need for dialysis, suspicion of non-bacterial pneumonia, obstructive pneumonia due to suspicion of cancer, immunodeficiencies, drug interaction and survival <72h 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/12h) 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

A.



B.

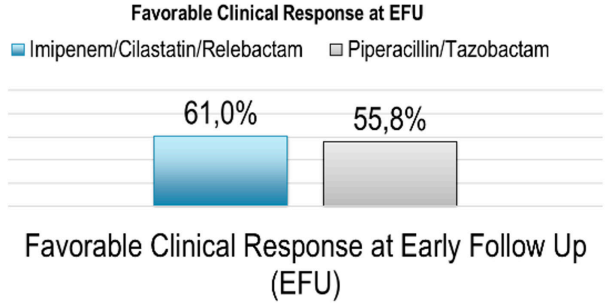


Figure 1 | **RESTORE IMI-2 Study: A) Day 28 all-cause mortality rate. B) Favorable Clinical Response at early follow up (EFU).**

and at 28 days. The identification and susceptibility of pathogens were confirmed in the central reference laboratory. Intermediate-susceptible pathogens were classified as non-susceptible.

The primary endpoint of the study was mortality at 28 days from any cause, the secondary endpoint of favorable clinical response in EFU (favorable with clinical resolution or unfavorable). Other secondary objectives were mortality at 28 days in the different subgroups, microbiological response (eradication or persistence of pathogens) in EOT and EFU. Mean treatment duration was 8,7 IMI/REL and 8,3 days with PIP/TAZ. The study was carried out in 113 hospitals of 27 countries from January 2016 to April 2019, 535 patients were randomized (266 IMI/REL, 269 PIP/TAZ). 66.1% were in intensive care units, 48.6% had ventilated HAP/VAP, 42.9% were >65 years, and 24.7% had moderate/severe renal impairment. The most frequent bacteria isolated were *K. pneumoniae* (25.6%), *P. aeruginosa* (18.9%), *Acinetobacter calcoaceticus-baumannii* complex (15.7%) and *E. coli* (15.5%) [10].

IMI/REL was noninferior to PIP/TAZ (Figure 1A and 1B) for the primary endpoint of mortality at day 28 (15.9% vs 21.3%; adjusted a treatment difference -5.3% [95% CI -11.9% to 1.2%]; no inferiority p<0.001). In the subgroups of ventilated HAP/VAP as well as in the subgroup of patients with APACHE II score ≥ 15, mortality was lower with IMI/REL than PIP/TAZ. IMI/REL was also noninferior for the key secondary endpoint of favorable clinical response (61% vs 55.8%) p<0,001 (adjusted treatment difference, 5% (95% CI -3.2% to 13.2%). In the different subgroups of patients, they were comparable, except in those with APACHE II score ≥ 15, where the clinical response was higher in IMI/REL. In the other secondary endpoints, overall microbiologic response at EFU, outcome was comparable between treatments. Most patients (85% vs 86.6%) had more than 1 adverse effect, more frequent in IMI/REL were diarrhea and increased transaminases. 6 patients with IMI/REL and 4 with PIP/TAZ discontinued treatment [10].

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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