Imipenem/cilastatin/relebactam: A new carbapenem β-lactamase inhibitor combination

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Purpose. The pharmacology, pharmacokinetics, pharmacodynamics, antimicrobial activity, efficacy, safety, and current regulatory status of imipenem/cilastatin/relebactam are reviewed.

Summary. Imipenem/cilastatin/relebactam is a newly approved anti-infective combination of a well-established β-lactam and a new β-lactamase inhibitor for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis, and complicated intra-abdominal infections (cIAIs) caused by susceptible gram-negative bacteria in patients 18 years of age or older with limited or no alternative treatment options. The antibiotic is also indicated for the treatment of hospital-acquired bacterial pneumonia (HABP) and ventilator-associated bacterial pneumonia (VABP). The antibiotic is active in vitro against a wide range of pathogens, including multidrug-resistant (MDR) *Pseudomonas aeruginosa* and carbapenem-resistant Enterobacterales (CRE) such as *Klebsiella pneumoniae* carbapenemase. The addition of relebactam does not restore the activity of imipenem against metallo-β-lactamase (MBL)–producing Enterobacterales and carbapenem-resistant *Acinetobacter baumannii*. Two phase 3 clinical trials of imipenem/cilastatin/relebactam were conducted. In the RESTORE-IMI 1 trial, the efficacy and safety of imipenem/cilastatin/relebactam was found to be comparable to that of imipenem/cilastatin plus colistin for the treatment of infections caused by imipenem-nonsusceptible gram-negative bacteria in patients with HABP/VABP, cUTIs, and cIAIs, with a significantly lower incidence of nephrotoxicity reported with the new antibiotic. The RESTORE-IMI 2 trial demonstrated the noninferiority of imipenem/cilastatin/relebactam to piperacillin/tazobactam for the treatment of HABP/VABP. Commonly reported adverse events in clinical trials included anemia, elevated liver enzymes, electrolyte imbalances, nausea, vomiting, diarrhea, headache, fever, phlebitis and/or infusion-site reactions, and hypertension.

Conclusion. Imipenem/cilastatin/relebactam is a new β-lactam/β-lactamase inhibitor combination with activity against MDR gram-negative bacteria, including many CRE but excluding MBL-producing Enterobacterales and carbapenem-resistant *Acinetobacter* baumannii. It is approved for the treatment of cUTIs, cIAIs, and HABP/VABP.

Keywords: β-lactam/β-lactamase inhibitor, imipenem/cilastatin, intraabdominal infection, pneumonia, relebactam, urinary tract infection

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Gram-negative bacteria are a common cause of serious infections.[1] According to the Centers for Disease Control and Prevention and the World Health Organization (WHO), many gram-negative bacteria are multidrug-resistant (MDR) and constitute a major global health threat.[2-4] In particular, nosocomial infections caused by MDR organisms, including carbapenemase-resistant bacteria, have been associated with prolonged hospital stay and increased mortality.[1,5] Such resistant bacteria are

not responsive to standard β-lactam antibiotics.[2,6-9] In addition, the use of antibiotics such as colistin, fosfomycin, and tigecycline has been hindered by their suboptimal efficacy, adverse effects, pharmacokinetic profiles, and increased rates of resistance.[10-12] Although carbapenems are effective against many MDR bacteria, including extended-spectrum β-lactamase (ESBL)–producing gram-negative bacteria, resistance to carbapenems has been rising, with a 5-fold increase in the last decade warranting the development of new agents.[13,14] Therefore, there is increasing interest in developing novel β-lactam/β-lactamase inhibitor combinations in order to overcome resistant bacteria, including carbapenemase-resistant Enterobacterales (CREs), *Pseudomonas aeruginosa* and *Acinetobacter baumannii*.[15,16] Imipenem/cilastatin/relebactam (Recarbrio, Merck & Co., Inc.) was approved by the Food and Drug Administration (FDA) in July 2019 for the treatment of complicated urinary tract infections (cUTIs), including pyelonephritis and complicated intra-abdominal infections (cIAIs) caused by susceptible bacteria in patients who are 18 years of age and older who have limited or no alternative treatment options.[17] In June 2020, the drug gained FDA approval for the treatment of hospital-acquired or ventilator-associated bacterial pneumonia (HABP or VABP).[18] Imipenem/cilastatin is effective against many MDR infections, including those caused by ESBL-producing gram-negative bacteria; however, rates of resistance to imipenem/cilastatin have been on the rise in the last 2 decades.[19] The addition of relebactam, an inhibitor of class A and class C β-lactamases, restored the activity of imipenem against MDR *P. aeruginosa* and many CREs, including *Klebsiella pneumoniae* carbapenemase (KPC).[20,21] This article reviews the pharmacology, mechanisms of resistance, in vitro activity, pharmacokinetic and pharmacodynamic properties, clinical efficacy, safety, and potential role in therapy of imipenem/cilastatin/relebactam. Recarbrio received the qualified infectious disease product (QIDP) designation, which is given to antibacterial and antifungal drug products intended to treat serious or life-threatening infections under the Generating Antibiotic Incentives Now (GAIN) act. As part of conferral of the QIDP designation, Recarbrio was granted priority review by FDA.

KEY POINTS

- Imipenem/cilastatin/relebactam is a new carbapenem β-lactamase inhibitor combination with activity against multidrug-resistant gram-negative organisms.
- The combination product is indicated for use in patients 18 years of age and older who have limited or no alternative treatment options for the treatment of complicated urinary tract infections, complicated intraabdominal infections, and hospital-acquired or ventilator-associated bacterial pneumonia caused by susceptible gram-negative bacteria.
- The most common adverse effects of the triple-drug medication include anemia, elevated liver enzymes, electrolyte imbalances, nausea, vomiting, diarrhea, headache, fever, phlebitis or infusion-site reactions, and hypertension.

Literature review

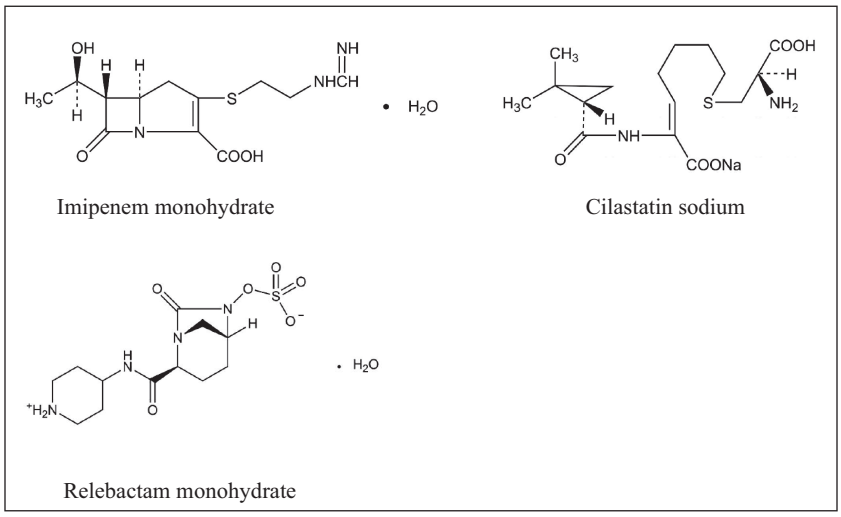
Available in vitro and preclinical studies, as well as phase 1, 2, or 3 clinical studies published in English between 2000 and June 2020 were reviewed to summarize the chemistry, pharmacology, efficacy, and safety of imipenem/cilastatin/relebactam in the treatment of gram-negative organisms.

Pharmacology and resistance

Imipenem is a bactericidal antibiotic that belongs to the carbapenem class. It acts by binding to and inhibiting the action of penicillin-binding proteins (PBPs), namely PBP 2 and PBP 1b, in Enterobacterales and *P. aeruginosa*, leading to the disruption of bacterial cell wall synthesis. Both cilastatin and relebactam lack intrinsic antibacterial activities. Cilastatin is a renal dehydropeptidase inhibitor that limits the renal metabolism and breakdown of imipenem, extending its antibacterial activity.[17] The newly added entity relebactam is a new β-lactamase inhibitor. Although imipenem is stable in the presence of many β-lactamases, relebactam protects imipenem from degradation by certain serine β-lactamase types, such as sulfhydryl variable (SHV), temoneira (TEM), cefotaximase-Munich (CTX-M), *Enterobacter cloacae* P99, *Pseudomonas*-derived cephalosporinase (PDC), class C cephalosporinases (eg, AmpC) and KPC (Figure 1).[17,22]

The mechanisms of β-lactam resistance in gram-negative organisms include the production of β-lactamases, upregulation of efflux pumps, and loss of outer membrane porins. Imipenem/cilastatin/relebactam retains activity in the presence of efflux pumps.[23] Imipenem/cilastatin/relebactam has shown activity against some isolates of *P. aeruginosa* and Enterobacterales that produce relebactam-susceptible β-lactamases concomitant with loss of entry porins. Imipenem/cilastatin/relebactam is not active against isolates containing metallo-β-lactamases (MBLs), some oxacillinases with carbapenemase activity, and certain alleles of Guiana extended-spectrum β-lactamase (GES). Genotypically characterized *P. aeruginosa* isolates that are not susceptible to imipenem/cilastatin/relebactam encoded some MBL, KPC, *Pseudomonas* extended resistance (PER), GES, Vietnamese extended-spectrum β-lactamase (VEB), and *Pseudomonas*-derived cephalosporinase (PDC) alleles. Imipenem is not active against methicillin-resistant *Staphylococcus aureus* (MRSA). Imipenem is not active in

Figure 1. Chemical structures of imipenem monohydrate, cilastatin sodium, and relebactam monohydrate.[17]



vitro against most isolates of *Enterococcus faecium*, *Stenotrophomonas maltophilia*, and some isolates of *Burkholderia cepacia*. No cross-resistance with other classes of antimicrobials has been identified. Some isolates resistant to carbapenems (including imipenem) and to cephalosporins may be susceptible to imipenem/cilastatin/relebactam.[17]

Spectrum of activity

With the emergence of resistance to imipenem and in an effort to restore its clinical activity, relebactam was combined with imipenem/cilastatin. Relebactam, a novel β-lactamase inhibitor, is a piperidine analogue diazobicyclo-octane that is designed to have inhibitory activity against class A β-lactamases, including KPC-type carbapenemases and class C β-lactamases.[24-28] To date, few published surveillance studies of imipenem/cilastatin/relebactam have included data describing in vitro activity.[21,24,26-33] Some of those studies were conducted as part of the Study for Monitoring Antimicrobial Resistance Trends (SMART) global surveillance program. Most of the results showed that *P. aeruginosa, K. pneumonia*, and *Enterobacter* species that were non–imipenem susceptible gained susceptibility with use of imipenem/cilastatin/relebactam. Imipenem/cilastatin/relebactam restored imipenem susceptibility when used against KPC and carbapenem-resistant *P. aeruginosa*, for which anticipated susceptibility is more than 80%. For OXA-48–like carbapenemase producers, the anticipated susceptibility to imipenem/cilastatin/relebactam is 30% to 80%. However, *A. baumaunii* isolates were resistant to imipenem/cilastatin and imipenem/cilastatin/relebactam.

Furthermore, imipenem/cilastatin/relebactam has been shown to be active in vitro and in clinical trials against several aerobic gram-negative bacteria, such as *Klebsiella* species, *E. cloacae*, *Escherichia coli, K. pneumoniae, Citrobacter freundii,* and *P. aeruginosa*, and against anaerobic gram-negative bacteria such as *Bacteroides* species, *Fusobacterium nucleatum,* and *Parabacteroides distasonis*. It has also been shown to be active against *Enterococcus faecalis*, methicillin-susceptible *S. aureus, Streptococcus anginosus*, and *Streptococcus constellatus*.[17] Additionally, the spectrum of activity includes gram-negative bacteria such as *Citrobacter koseri* and *Enterobacter asburiae* and anaerobic bacteria such as *Eggerthella lenta Parvimonas micra, Peptoniphilus harei, Peptostreptococcus anaerobius, Fusobacterium necrophorum, Fusobacterium varium, Parabacteroides goldsteinii, Parabacteroides merdae, Prevotella bivia,* and *Veillonella parvula*.[17] Table 1 summarizes the in vitro inhibitory activity of imipenem/cilastatin/relebactam.

Pharmacokinetics and pharmacodynamics

The pharmacokinetic profile of relebactam following a single-dose administration was found to be similar to that of imipenem.[20] Its observed half-life ($t_{½}$) was comparable to that of imipenem (1.39-1.84 hours vs 1.1 hours). Such comparable half-life data support the administration of imipenem/cilastatin/relebactam every 6 hours (similar to the schedule for imipenem/cilastatin).[20] Moreover, other pharmacokinetic parameters, such as area under the curve (AUC) and concentration at end of infusion (C_{EOI}), were similar when relebactam was dosed with and without imipenem/cilastatin, with no detection of any drug–drug interaction.[20] Also, following single-dose administration of relebactam to elderly individuals and adult women, there was no clinically relevant impact on relebactam pharmacokinetics. Following administration of multiple doses of relebactam, the terminal $t_{½}$ was similar on days 1 and 7. When relebactam was coadministered with imipenem/cilastatin every 6 hours for 14 days, similar pharmacokinetic parameters were noted. Therefore, the pharmacokinetic parameters were similar after single- and multiple-dose administration, with insignificant accumulation. The percentage of the dosing interval during which unbound plasma concentrations of imipenem exceed the imipenem/cilastatin/relebactam minimum inhibitory concentration (MIC) (ie, *f*T>MIC) against the infecting organism best correlates with antibacterial activity in animal and in vitro models of infection.[34] The ratio of the 24-hour unbound plasma relebactam AUC to the imipenem/cilastatin/relebactam MIC (ie, $fAUC_{0\text{-}24}$/MIC) best predicts the activity of relebactam in animal and in vitro models of

Table 1. In Vitro Activity of Imipenem/Cilastatin/Relebactam Against Gram-negative Pathogens[21,25,27,28,31]

Organism (s)	MIC_{90}, µg/mL	MIC Range, µg/mL	% Susceptible
All *P. aeruginosa* (*n* = 845)[a]	2	0.06 to >32	94.2
Imipenem nonsusceptible *P. aeruginosa* (*n* = 251)[a]	4	0.25 to >32	80.5
All *P. aeruginosa* (*n* = 5447)[b]	4	≤0.03 to >32	92.4
Imipenem-nonsusceptible *P. aeruginosa* (*n* = 1902)[b]	>32	≤0.03 to >32	78.2
All *P. aeruginosa* (*n* = 490)[c]	2/4	≤0.03/4 to >16/4	98
Imipenem-nonsusceptible *P. aeruginosa* (*n* = 144)[c]	2/4	0.25/4 to >16/4	92
All *K. pneumoniae* (*n* = 689)[a]	0.5	≤0.03 to 4	99
Imipenem nonsusceptible *K. pneumoniae* (*n* = 27)[a]	2	0.06-4	74.1
All *K. pneumoniae* (*n* = 891)[c]	0.25/4	0.06/4 to 2/4	99.3
Imipenem-nonsusceptible *K. pneumoniae* (*n* = 111)[c]	1/4	0.12/4 to 2/4	97
Imipenem-nonsusceptible *K. pneumoniae* (*n* = 314)[d]	1	1 to >64	98
Enterobacter spp. (*n* = 399)[a]	0.5	≤0.03 to 1	100
Imipenem-nonsusceptible *Enterobacter* (*n* = 8)[a]	NA	0.12 to 1	100
Enterobacter spp. (*n* = 211)[c]	0.5	≤0.03/4 to 2/4	99
E. coli (*n* = 2,778)[c]	0.25/4	≤0.03/4 to 1/4	100
A. baumannii (*n* = 72)[a]	>32	0.12 to >32	45.8
A. baumannii (*n* = 158)[c]	>16/4	≤0.03/4 to >16/4	51
Imipenem-resistant *A. baumannii* (*n* = 58)[c]	>16/4	≤0.03/4 to >16/4	12

Abbreviations: MIC_{90}, minimum inhibitory concentration for 90% of tested isolates; NA, not applicable.
[a]Source: Study for Monitoring Antimicrobial Resistance Trends (SMART) surveillance program, 2015 US data.
[b]Source: SMART surveillance program, 2015–2017 European data.
[c]Separate values reported for imipenem and relebactam, with relebactam MIC_{90} reported as a constant, at 4 µg/L. Source: Lapuebla et al, US data.
[d]Source: data from Greek hospitals, 2015-2016.

infection.[17,34] In a study of healthy subjects, the penetration into the epithelial lining fluid (ELF) was similar for imipenem and relebactam.[35] Table 2 summarizes imipenem/cilastatin/relebactam pharmacokinetics after a 30-minute infusion.

Clinical efficacy

Phase 2 trials. Lucasti et al[36] conducted a phase 2 randomized, multicenter, double-blind controlled trial to compare the safety and efficacy of 2 relebactam doses (125 and 250 mg, each given every 6 hours) plus imipenem/cilastatin 500 mg vs imipenem/cilastatin plus placebo for the treatment of cIAIs. Among 255 patients who were included in the microbiologically evaluable (ME) analysis, the proportion of subjects in the ME population with a favorable clinical response was generally similar among the 3 treatment groups, ranging from 95.2% to 98.8%. Both doses of relebactam plus imipenem/cilastatin were noninferior to imipenem/cilastatin alone with respect to the clinical response rate at the discontinuation of intravenous (IV) study therapy (DCIV) visit. Clinical response rates in the microbiological intention to treat (MITT) population were consistent with those of the ME population. Among the patients who were treated with imipenem/cilastatin/relebactam, the reported success rates against specific pathogens (as demonstrated by favorable clinical response at DCIV) were as follows: *P. aeruginosa*, 100%; *K. pneumoniae*, 100%; *E. cloacae*, 100%; *Proteus mirabilis*, 100%; and *E. coli*, 96.4%.[36]

Another phase 2 randomized, multicenter, double-blind controlled trial, conducted by Sims et al,[37] compared the efficacy, safety, and tolerability of 2 doses of relebactam (250 and 125 mg) plus imipenem/cilastatin vs placebo plus imipenem/cilastatin in adult patients with cUTIs, which were not limited to infections involving MDR pathogens. Among 230 patients who were included in the ME analysis, more than 95% of ME patients in each treatment arm had favorable microbiological responses at the DCIV visit: 95.5% of those treated with imipenem/cilastatin/relebactam 250 mg, 98.6% of those treated with imipenem/cilastatin/relebactam 125 mg, and 98.7% of those who received imipenem/cilastatin plus placebo. Both the 250 mg and 125 mg doses of relebactam, combined with imipenem/cilastatin, were noninferior to imipenem/cilastatin plus placebo. At the DCIV visit, favorable clinical response rates in ME patients were generally similar across treatment groups.

Composite clinical and microbiological response rates at early follow-up (EFU) were also similar across treatment groups. Among the patients who were treated with imipenem/cilastatin/relebactam, the following were the reported in vitro susceptibility rates for specific pathogens at DCIV: *P. aeruginosa*, 93.8%; *K. pneumoniae*, 100%; *E. cloacae*; 100%; *P. mirabilis*, 54.5%; *C. freundii*, 100%; and *E. coli*, 100%.[37]

Phase 3 trials. The RESTORE-IMI 1 trial was a phase 3 randomized, double-blind study in which Motsch et al[38] evaluated the efficacy and safety of imipenem/cilastatin/relebactam vs imipenem/cilastatin plus colistin for treatment of imipenem-nonsusceptible serious, gram-negative bacterial infections. Patients who were hospitalized and required IV antibacterial treatment for VABP, cUTIs, or cIAIs were randomly assigned in a 2:1 ratio to receive IV imipenem/cilastatin/relebactam (500 and 250 mg of imipenem and relebactam, respectively) every 6 hours plus placebo or IV imipenem/cilastatin (500 mg every 6 hours) plus colistimethate sodium (a loading dose to achieve 300 mg of colistin base activity, followed by maintenance doses of up to 150 mg of colistin base activity every 12 hours). The minimum treatment duration was 5 days (for cIAIs and cUTIs) or 7 days (for HABP and VABP), with a maximum treatment duration of 21 days. The primary efficacy endpoint was overall response in the microbiologic modified intent-to-treat (mMITT) population of patients infected with a qualifying baseline pathogen who received at least 1 dose of a study treatment. The overall response was defined differently for each infection type, as follows: for HABP or VABP, 28-day all-cause mortality; for cIAI, clinical response on day 28; and for cUTI, composite clinical and microbiologic response at EFU. The incidence of adverse events was another primary endpoint in the safety population. Forty-seven patients were enrolled from 16 sites in 11 countries. The mMITT population comprised 31 patients (11 with HABP or VABP, 16 with cUTIs, and 4 with cIAIs), of whom 35% were 65 years of age or older. Rates of prior antibacterial therapies were largely comparable between the study arms, but prior meropenem therapy was more frequent in imipenem/cilastatin/relebactam-treated patients. Qualifying baseline pathogens in mMITT patients were *P. aeruginosa* (77%), Klebsiella species (16%), and other Enterobacterales (6%). Detected β-lactamases included AmpC (84% of mMITT patients), ESBLs (35%), KPC (16%), and OXA-48 β-lactamases (3%). The efficacy outcomes are summarized in Table 3. The study concluded that imipenem/cilastatin/relebactam may be preferable to colistin-based therapy for treating carbapenem-nonsusceptible infections, given that imipenem/cilastatin/relebactam had comparable efficacy but was associated with a significantly lower incidence

Table 2. Pharmacokinetics of Relebactam Dosed in Combination with Imipenem/Cilastatin After 30-Minute Infusion[35]

Parameter	Value
C_{max} (mg/L)	30.5/15.8
$t_{½}$ (h)	1.13/1.63
Vd (L)	19.6/20.8
$AUC_{0\text{-inf}}$ (mg · h/L)	130/81.2
CL (L/h)	12.1/8.9
Elimination (%)	49.8/>95.0
ELF penetration (%)	55/54

Abbreviations: C_{max}, maximum concentration; $t_{½}$, half-life; Vd, volume of distribution; $AUC_{0\text{-inf}}$, area under the curve from time 0 extrapolated to infinite time; CL, clearance; ELF, epithelial lining fluid.

Table 3. Efficacy Outcomes in the RESTORE-IMI 1 Trial[38]

Outcome and Infection Site	Imipenem/Cilastatin/Relebactam (*n* = 21)	Imipenem/Cilastatin plus Colistin (*n* = 10)	Adjusted Difference 90% CI
Favorable overall response	71.4	70	–27.5 to 21.4
HABP/VABP	87.5	66.7	NA
cIAI	0	0	NA
cUTI	72.7	100	–52.8 to 12.8
Favorable clinical response at day 28	71.4	40	1.3-51.5
28-day all-cause mortality	9.5	30	–46.4 to 6.7

Abbreviations: CI, confidence interval; cIAI, complicated intra-abdominal infection; cUTI, complicated urinary tract infection; HABP, hospital-acquired bacterial pneumonia; NA, not applicable; VABP, ventilator-acquired bacterial pneumonia.

of nephrotoxicity and other adverse events.[38]

The RESTORE-IMI 2 trial was a recent phase 3 global, multicenter, randomized, comparator-controlled noninferiority trial.[18] It compared the efficacy and safety of imipenem 500 mg plus relebactam 250 mg plus cilastatin 500 mg IV vs piperacillin/tazobactam 4.5 g IV every 6 hours, with both regimens administered for 7 to 14 days in adult patients with HABP or VABP. Empiric linezolid therapy (600 mg IV every 12 hours) was delivered until baseline cultures confirmed the absence of MRSA. The primary outcome was all-cause mortality at day 28, and the key secondary endpoint was clinical response at EFU (7-14 days after completion of therapy) in the MITT population (patients who received at least 1 dose of study drug after randomization, excluding patients with only gram-positive cocci present on baseline Gram stain). The study findings, presented at the European Congress of Clinical Microbiology and Infectious Diseases, showed in the MITT population that 48.6% had ventilated HABP or VABP, 42.9% were 65 years of age or older, 66.1% were in the intensive care unit, 47.5% had Acute Physiology And Chronic Health Evaluation II (APACHE II) scores of ≥15, and 24.7% had moderate or severe renal impairment. *K. pneumoniae* (25.6%), *P. aeruginosa* (18.9%), *A. calcoaceticus-baumannii* complex (15.7%), and *E. coli* (15.5%) were the most common causative pathogens in the microbiologic MITT population. Imipenem/cilastatin/relebactam was noninferior ($P < 0.001$) to piperacillin/tazobactam for both primary and key secondary efficacy endpoints.[18,39,40]

Trial limitations. In the phase 2 trial of Lucasti et al,[36] a small number of resistant pathogens were identified. Patients who were most severely ill (APACHE II score of >30) or had moderate to severe renal insufficiency (creatinine clearance [CLcr] of <50 mL/min) were excluded. In the trial of Sims et al,[37] the imipenem backbone was the same across treatment arms, which complicated the assessment of the true efficacy of relebactam when used in combination with imipenem/cilastatin. This trial included a large number of patients with less severe infections not caused by MDR organisms, while imipenem/cilastatin/relebactam mostly targets MDR infections. In the RESTORE-IMI 1 trial,[38] many patients received extensive pretrial antibacterial therapy and had high APACHE II scores. The lack of favorable response may have been due to indeterminate responses or patients' medical complexity. Additionally, the renally adjusted colistin dose was not compliant with published guidelines[40]; this might have affected the safety and/or efficacy results. Furthermore, a small number of patients with CRE infections were recruited into the trials, thus limiting the generalizability of the findings to a narrow patient population.

Safety and tolerability

The safety of imipenem/cilastatin/relebactam, administered via injection, was studied by Lucasti et al[36] and Sims et al.[37] In the cUTI and cIAI trials, patients received imipenem/cilastatin (500 mg/500 mg) plus relebactam 250 mg (approved dose), relebactam 125 mg (not an approved dose), or a placebo. Across both dose-ranging trials, the mean duration of IV therapy in patients treated with imipenem/cilastatin plus relebactam 250 mg was approximately 7 days. The most common adverse reactions observed in patients included nausea, diarrhea, headache, fever, and increased liver enzymes. In both trials, adverse reactions occurred during the protocol-specified follow-up period (ie, the period during and for 14 days after completion of IV therapy) in 39% (85 of 216) of patients receiving imipenem/cilastatin plus relebactam 250 mg and 36% (77 of 214) of patients receiving imipenem/cilastatin plus placebo.

In both trials, serious adverse reactions occurred in 3.2% (7 of 216) of patients receiving imipenem/cilastatin plus relebactam 250 mg and 5.1% (11 of 214) of patients receiving imipenem/cilastatin plus placebo. There were no deaths reported in patients receiving imipenem 500 mg/cilastatin 500 mg plus relebactam 250 mg or imipenem/cilastatin plus placebo. Deaths were reported in 1.4% (3 of 215) of patients receiving imipenem/cilastatin plus relebactam 125 mg (not an approved dose). Adverse reactions leading to discontinuation occurred in 1.9% (4 of 216) of patients receiving imipenem/cilastatin plus relebactam 250 mg and 2.3% (5 of 214) of patients receiving imipenem/cilastatin plus placebo.[17] In the phase 2 cIAI trial, adverse events leading to discontinuation were considered drug related in 1 subject who received relebactam 125 mg plus imipenem/cilastatin (that patient had a treatment-emergent decrease in CL_{cr}) and in 3 subjects who received imipenem/cilastatin alone (those patients had thrombocytosis, nausea, and increased alanine transaminase, respectively). The rates of discontinuation due to an adverse event were low overall and similar across treatment groups.[36] In the phase 2 cUTI trial, only 4 patients had treatment-related adverse events leading to discontinuation of the IV study drug: 2 of 99 (2.0%) who received imipenem/cilastatin and relebactam 250 mg (diarrhea in one patient, rash in another patient), 1 of 99 (1.0%) treated with imipenem/cilastatin and relebactam 125 mg (nausea) and 1 of 100 (1%) treated with imipenem/cilastatin alone (diarrhea). One patient in the relebactam 250 mg group experienced an aspartate transaminase elevation of more than 5 times the upper limit of normal.[37] In the RESTORE-IMI 1 trial, there were no patients in imipenem/cilastatin/relebactam group who discontinued the drug due to drug-related adverse effects.[38] In addition, Brown et al[41] evaluated nephrotoxicity retrospectively using 2 acute kidney injury assessment criteria (the Kidney Disease: Improving Global Outcomes [KDIGO] criteria and Risk, Injury, Failure, Loss, and End-stage Kidney Disease [RIFLE] criteria). Additional outcomes included time to onset of protocol-defined nephrotoxicity and incidence of renal adverse events. They showed that imipenem/cilastatin/relebactam has a more favorable safety

profile than colistin-based therapy.[41] In the RESTORE-IMI 2 trial, 6 patients (2.3%) discontinued imipenem/cilastatin/relebactam due to drug-related adverse effects. The rates of discontinuation due to an adverse event were low and similar across treatment groups.[39] Boundy et al[42] recently conducted a single-dose (1150 mg [ie, 4.6-fold above the 250-mg therapeutic dose]), double-blind (relebactam only), randomized, placebo- and positive-controlled, 3-period, balanced crossover study of healthy participants. Analysis of electrocardiogram parameters resulted in no additional cardiac safety concerns with relebactam compared to moxifloxacin. Overall, a supratherapeutic dose of relebactam yielded no cardiac safety events and was not associated with QT interval prolongation or other abnormal cardiodynamic parameters.

Table 4 include the safety outcomes of imipenem/cilastatin/relebactam derived from clinical trials.

Imipenem/cilastatin/relebactam is associated with drug interactions with other antimicrobials. In vitro studies have demonstrated no antagonism between imipenem/cilastatin/relebactam and amikacin, azithromycin, aztreonam, colistin, gentamicin, levofloxacin, linezolid, tigecycline, tobramycin, or vancomycin.[17] When imipenem/cilastatin was given concomitantly with ganciclovir, generalized seizures were reported. Therefore, ganciclovir should not be used concomitantly with imipenem/cilastatin/relebactam unless the potential benefits outweigh the risks.[17] The concomitant use of carbapenems, including imipenem/cilastatin, with valproic acid or divalproex sodium may decrease valproic acid concentrations, which may increase the risk of breakthrough seizures. Although the mechanism of this interaction is unknown, data from in vitro and animal studies suggest that carbapenems may inhibit the hydrolysis of valproic acid's glucuronide metabolite (VPA-g) back to valproic acid, thus decreasing the serum concentrations of valproic acid. Thus, the concomitant use of imipenem/cilastatin/relebactam with valproic acid or divalproex sodium should be avoided. Clinicians should consider alternative antibacterials (ie, agents other than carbapenems) to treat infections in patients whose seizures are well controlled with use of valproic acid or divalproex sodium.[17]

To date, data on pregnant and lactating mothers is lacking; this warrants weighing the risks and benefits of imipenem/cilastatin/relebactam to pregnant women and lactating mothers and their infants prior to prescribing.[17] Imipenem/cilastatin/relebactam has not been studied in individuals younger than 18 years.[17] In geriatric patients (≥65 years of age), data from clinical trials show that renal dosage adjustment is not necessary.[17]

Dosing, administration, and cost

The recommended dosage of Recarbrio in adults with normal renal function is 1.25 g (imipenem 500 mg, cilastatin 500 mg, and relebactam 250 mg) administered intravenously over 30 minutes every 6 hours.[17] The recommended duration of therapy is 4 to 14 days as guided by the severity and site of infection as well as the clinical response. The dosage should be

Table 4. Safety Outcomes in Clinical Trials of Imipenem/Cilastatin/Relebactam[18,39]

Clinical Trial	Adverse Effect	Incidence, %
Phase 2 cIAI trial[34]	Nausea	6.8
	Vomiting	6
	Diarrhea	6
	Increased liver enzymes (alanine and aspartate transferases, alkaline phosphatase)	2.6
Phase 2 cUTI trial[35]	Headache	7.1
	Diarrhea	5.1
	Nausea	4
	Increased liver enzymes (alanine and aspartate aminotransferases)	3
	Fever	2
RESTORE IMI-1 trial[36]	Increased liver enzymes (alanine and aspartate aminotransferases, γ-glutamyl transferase, alkaline phosphatase)	22.6
	Fever	12.9
	Nausea	6.5
	Decreased creatinine renal clearance	6.5
	Infusion-site phlebitis	3.2
RESTORE IMI-2 trial	Increased liver enzymes (alanine and aspartate aminotransferases)	6.4
	Diarrhea	2.3

adjusted in patients with renal impairment, defined as a CL_{cr} of <90 mL/min. The recommended dosage is 1 g (imipenem 400 mg, cilastatin 400 mg, and relebactam 200 mg) every 6 hours in patients with a CL_{cr} of 60 to 89 mL/min; 0.75 g (imipenem 300 mg, cilastatin 300 mg, and relebactam 150 mg) every 6 hours in patients with a CL_{cr} of 30 to 59 mL/min; and 0.5 g (imipenem 200 mg, cilastatin 200 mg, and relebactam 100 mg) every 6 hours in patients with a CL_{cr} of 15 to 29 mL/min and in patients with end-stage renal disease receiving hemodialysis.[17] Imipenem/cilastatin/relebactam should be administered after hemodialysis. Imipenem/cilastatin/relebactam is not recommended for patients with a CL_{cr} of <15 mL/min unless hemodialysis is started within 48 hours. No dosage adjustment recommendations are provided for patients undergoing peritoneal dialysis.

Recarbrio 1.25 g for injection is supplied as a white to light yellow, sterile dry powder in a single-dose vial that must be reconstituted and further diluted prior to administration. Each vial contains 500 mg of imipenem (anhydrate equivalent), 500 mg of cilastatin (free acid equivalent), and 250 mg of relebactam (anhydrate equivalent). Appropriate diluents include 0.9% sodium chloride, 5% dextrose, 5% dextrose plus 0.9% sodium chloride, 5% dextrose plus 0.45% sodium chloride, and 5% dextrose plus 0.225% sodium chloride. In order to prepare a solution for administration to a patient with normal renal function, it is recommended to withdraw two 10-mL aliquots of diluent from a 100-mL infusion bag containing an appropriate diluent, constitute the vial with one 10-mL aliquot of diluent, shake well, transfer to the remaining 80 mL of the infusion bag, add the second 10-mL aliquot of diluent to the vial, shake well, and transfer to the infusion solution. The resulting 100-mL mixture should be agitated until clear. The color of the reconstituted solution ranges from clear to yellow. After dilution, imipenem/cilastatin/relebactam is stable for at least 2 hours at room temperature (up to 30°C) or at least 24 hours under refrigeration (2°C-8°C). Solutions of imipenem/cilastatin/relebactam should not be frozen. Imipenem/cilastatin/relebactam is compatible with a wide range of intravenous medications; however, it is incompatible with propofol in 5% dextrose or 0.9% sodium chloride, amphotericin B deoxycholate, and posaconazole.[17,43,44]

The average wholesale price (AWP) of 1 day of treatment with imipenem/cilastatin/relebactam is $1,284, which is roughly comparable to that of other new β-lactam/β-lactamase inhibitors (the AWP of 1 day of treatment with ceftazidime/avibactam is $1,291.71, and the AWP of 1 day of treatment with meropenem/vaborbactam is $1,283.04).[45-47] However, as of the time of writing there were no published pharmacoeconomic studies of imipenem/cilastatin/relebactam.

Place in therapy

The addition of relebactam, a novel β-lactamase inhibitor with dual class A/C activity, to imipenem/cilastatin, an established antipseudomonal carbapenem, restores in vitro activity of imipenem against many gram-negative organisms, notably Enterobacterales (including many carbapenem-resistant strains) and *P. aeruginosa* (including MDR strains). The addition of relebactam does not confer activity against class B MBL, class D OXA-48–producing Enterobacterales, and carbapenem-resistant *A. baumannii*. Phase 2 clinical trials have shown that imipenem/cilastatin/relebactam is noninferior to imipenem/cilastatin in the treatment of adult patients with cUTIs, including pyelonephritis, and cIAIs. Adverse reactions in patients receiving imipenem/cilastatin/relebactam were comparable to those in patients receiving imipenem/cilastatin. A small phase 3 clinical trial has shown that imipenem/cilastatin/relebactam is an efficacious and well-tolerated option compared to imipenem/cilastatin plus colistin for the treatment of HABP/VABP, cIAIs, and cUTIs caused by imipenem-nonsusceptible (but imipenem/cilastatin/relebactam- and colistin-susceptible) gram-negative organisms. As expected, imipenem/cilastatin/relebactam was associated with significantly lower rates of nephrotoxicity than imipenem/cilastatin plus colistin. Another phase 3 clinical trial has shown that imipenem/cilastatin/relebactam is noninferior to piperacillin/tazobactam in the treatment of adult patients with HABP/VABP. Adverse reactions in patients receiving imipenem/cilastatin/relebactam were comparable to those in patients receiving piperacillin/tazobactam. Additionally, since imipenem/cilastatin has been studied in patients with neutropenic fever, the new antibiotic may be used in this patient population for the treatment of MDR organisms.[48]

According to the principle of judicious and appropriate use of antibiotics, imipenem/cilastatin/relebactam should be reserved for the treatment of infections caused by gram-negative organisms that are resistant to other available agents, although imipenem/cilastatin/relebactam should be considered before polymyxins for the treatment of CRE infections, particularly in patients at high risk for nephrotoxicity. Clinical trials, availability of other new agents active against resistant gram-negative organisms, and cost will determine the specific role of imipenem/cilastatin/relebactam in the treatment of gram-negative infections.

Conclusion

Imipenem/cilastatin/relebactam, a new carbapenem β-lactamase inhibitor combination, is indicated for use in patients 18 years of age or older for the treatment of HABP/VABP caused by susceptible gram-negative bacteria. It is also indicated for use in patients 18 years of age or older who have limited or no alternative treatment options for the treatment of cUTIs and cIAIs caused by susceptible gram-negative bacteria. Imipenem/cilastatin/relebactam should be reserved for the treatment of gram-negative infections that are resistant to other available agents.

Disclosures

Dr Chahine served on the speakers bureau of Merck and on the advisory board of Theratechnologies. The other authors have declared no potential conflicts of interest.

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