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BRIEF REPORT

Real-World Experience of Imipenem–Relebactam Treatment as Salvage Therapy in Difficult-to-Treat *Pseudomonas aeruginosa* Infections (IMRECOR Study)

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ABSTRACT

***Introduction*:** Difficult-to-treat-resistant (DTR) infections caused by *Pseudomonas aeruginosa* represent a global public health threat, prioritizing the search and development of new antibiotics for this microorganism.

***Methods*:** We present the real-life experience of the compassionate use of imipenem/cilastatin/relebactam in a descriptive study involving 14 patients with DTR-*P. aeruginosa* infection and limited treatment options.

***Results*:** The primary source of infection was skin and soft tissue infection, 57.1% (8/14), followed by

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respiratory infection-pneumonia, 28.6% (4/14). At the onset of infection, 71.4% (10/14) of patients were in the intensive care unit (ICU). All our patients had a Charlson Score of ≥ 3. Septic shock was observed in 64.3% (9/14) of patients. The median treatment duration was 15 days, and no patient experienced an adverse event that required treatment interruption. All-cause 30-day mortality was observed in 42.9% of cases (6/14), while clinical efficacy and microbiological success were observed in 64.3% (9/14).

***Conclusions*:** Imipenem/cilastatin/relebactam may represent a treatment option for patients with DTR-*P. aeruginosa* infections, which should be validated in prospective clinical trials.

Keywords: *Pseudomonas aeruginosa*; Imipenem; Cilastatin; Relebactam; Carbapenem; Resistant; Multidrug; Resistant

Key Summary Points

Infections caused by drug-resistant *Pseudomonas aeruginosa* represent a global public health threat.

It is essential to pursue new antibiotics that provide a more effective and safe treatment option for patients with drug-resistant *Pseudomonas aeruginosa* infections.

Imipenem/cilastatin/relebactam exhibits good activity against difficult-to-treat resistant *Pseudomonas aeruginosa* infections.

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The favorable tolerance of imipenem/cilastatin/relebactam, along with its low toxicity, positions this antibiotic as a viable treatment option for patients with drug-resistant *Pseudomonas aeruginosa* infections.

INTRODUCTION

Given the growing threat posed by carbapenem-resistant pathogens and the increasing resistance to new antimicrobials, the search for new antibiotics for effective and safe treatment of *Pseudomonas aeruginosa* with difficult-to-treat resistant (DTR) is essential.

DTR-*P. aeruginosa* is a concept introduced in 2018 and refers to *P. aeruginosa* isolates not susceptible to any of the following antimicrobials: ceftazidime, cefepime, piperacillin-tazobactam, aztreonam, imipenem–cilastatin, meropenem, ciprofloxacin, and levofloxacin [1].

A recent study published in Spain, which included 3180 clinical isolates of *P. aeruginosa*, showed a DTR-*P. aeruginosa* rate of 2.1% in 2022. In this study, the resistance rate to IMR was 2.5%, with a higher rate of 5.3% in patients admitted to the intensive care unit (ICU) compared to 2.3% in non-ICU patients [2].

Imipenem/cilastatin/relebactam (IMR) combines the carbapenem imipenem, the renal dehydropeptidase-I inhibitor cilastatin, and the novel β-lactamase inhibitor, relebactam. Two phase III clinical trials evaluated the efficacy and safety of IMR. The phase III RESTORE-IMI 1 trial was a randomized, multicentric, double-blind study designed to compare the effectiveness and safety of IMR with imipenem plus colistin (COL) therapy for the treatment of hospital-acquired pneumonia/ ventilator-associated pneumonia (HAP/VAP), complicated intra-abdominal infection (cIAI) and complicated urinary tract infection (cUTI) caused by imipenem-non-susceptible isolates. This study showed a favorable overall response rate in both groups, with a better safety profile of IMR compared to colistin-based therapy for cIAI and cUTI [3]. In another phase III study, RESTORE IMI 2, a randomized, double-blind controlled study, IMR demonstrated

non-inferiority compared to piperacillin-tazobactam treatment in adult patients with HAP/VAP [4].

Although clinical trials are the gold standard for testing the effectiveness and safety of medical treatments, they often do not reflect the real-world use of antimicrobials in daily clinical practice. This study aims to report on the real-life experience of the compassionate use of IMR in patients with DTR-*P. aeruginosa* infection.

METHODS

This was a multicenter, retrospective, observational case series of patients with DTR-*P. aeruginosa* infection treated with IMR for at least 48 h under compassionate use following failure or intolerance of a primary active regimen (salvage therapy). Nine different hospitals from Spain participated. The IMR was only used under compassionate use in patients with DTR-*P. aeruginosa*. The data from the hospitals that requested this antimicrobial were provided directly by the Medical Department of Merck Sharp and Dohme (MSD) Spain.

The study was coordinated from Reina Sofia University Hospital, Córdoba, Spain, from July 2019 to March 2023 and was approved by the Ethics Committee (code 5317).

The primary outcome variable was all-cause 30-day mortality. Secondary outcomes included clinical efficacy and microbiological success at day 30. Clinical efficacy was defined as patient survival with resolution of signs and symptoms of infection at the end of treatment and absence of recurrence up to day 30 of follow-up. Microbiological success was defined as no growth of *P. aeruginosa* in cultures of clinical samples from the end of treatment until day 30 of follow-up. Patients who achieved clinical efficacy but could not be assessed for colonization were also considered microbiological success.

The following explanatory variables were collected from each patient: sex, age, chronic underlying diseases, source of infection, and severity of system inflammatory response at the presentation of the infection [5]. The Cockroft–Gault formula calculates creatinine clearance (CL_{CR}). Renal failure was defined as CL_{CR} < 60 ml/min. The need for an invasive procedure to control the focus of infection was also considered. Infections were determined according to the CDC criteria [6]. Additionally, any adverse events that occurred during treatment were reported.

We administered a standard dose of IMR: 500 mg imipenem/cilastatin with 250 mg relebactam every 6 h via intravenous infusion, adjusted for renal function as recommended by the summary of product characteristics of the European Medicines Agency (EMA SmPC). The investigator determined the duration of the treatment.

The clinical and microbiological diagnosis of the infection, including the initial identification and susceptibility testing of the isolates, were conducted at each participating center. *P. aeruginosa* were identified using MALDI-TOF (Bruker Diagnostics, Billerica, MA, USA). Additionally, when isolates were available ($n = 7$), they were further characterized in a centralized laboratory at the University Hospital Reina Sofia, Cordoba, Spain. Identification was confirmed again using MALDI-TOF (Bruker Diagnostics), and susceptibility testing was performed using the WalkAway semi-automated system (Beckman Coulter, Madrid, Spain) with MicroScan microdilution panels NC54, Sensititre™ EUMDROXF microdilution panels (Thermo Fisher Scientific, Waltham, MA, USA) and UMIC cefiderocol (Bruker Diagnostics) microdilution panels, following manufacturers' recommendations. Susceptibility testing results were interpreted according to EUCAST breakpoints [7]. Carbapenemase activity was detected using the modified carbapenem inactivation method (mCIM) [8] and the β-Carba™ test (Bio-Rad, Madrid, Spain). Additionally, carbapenemases were identified using the NG-Test CARBA 5 immunochromatography assay (Biotech, Madrid, Spain) and the Xpert Carba-R assay (Cepheid, Barcelona, Spain). Details regarding minimum inhibitory concentrations (MICs) against isolate #9 have been previously reported, and the corresponding data has also been included in this manuscript to provide comprehensive information [9].

RESULTS

Patient Characteristics

The study included 14 patients, with a median age of 58 (range 24–75).

At the onset of infection, 71.4% (10/14) of patients were in the ICU. The Charlson Comorbidity Score was ≥ 3 in 100% of patients. Septic shock was observed in 64.3% (9/14) of patients. Bacteremia was present in 28.4% of patients and among those with bacteremia, 50% (2/4) died. The primary source of infection was skin and soft tissue infection, 57.1% (8/14), followed by respiratory infection-pneumonia (28.6%), intra-abdominal infection (one patient), and one patient had a central nervous system infection (meningoventriculitis). Table 1 provides a detailed description of the cohort with DTR-*P. aeruginosa* infections treated with IMR.

Organism Characteristics

As presented in Table 2, all isolates were multidrug-resistant. They were all resistant to meropenem, and 12/14 were also resistant to imipenem. Among the seven isolates available for centralized testing, five were susceptible to IMR, one to meropenem–vaborbactam (MEV), and six to cefiderocol (FDC). None of the isolates produced carbapenemase. Seven out of 13 tested isolates were susceptible to ceftolozane/tazobactam (C/T), while only 2 out of 13 tested isolates were susceptible with increased exposure to ceftazidime/avibactam (CAZ-AVI).

Treatment Characteristics

IMR was used in monotherapy in all cases. All 14 patients had previously received antimicrobial treatment with clinical failure. Among them, 12 patients (85.7%) had received empirical treatment with carbapenems, with 11 patients receiving meropenem and one receiving both imipenem and meropenem. Additionally, nine patients had received previous targeted therapy with new β-lactam–β-lactamase inhibitor (BLBI) drugs, including CAZ-AVI, C/T, and FDC (Table 1).

The median duration of treatment was 15 days. Only one patient experienced a mild adverse effect during treatment: nausea. However, this adverse effect did not require a dose reduction or treatment interruption.

Patient Outcomes

The all-cause mortality at 30 days was 42.9% of cases (6/14). Clinical efficacy and microbiological success were observed in 64.3% of cases (9/14).

DISCUSSION

We describe the multicentric experience of compassionate use of IMR as salvage treatment for DTR-*P. aeruginosa* infections with limited therapeutic options. The all-cause 30-day mortality rate was 42.9%, which is higher than that described in a previous patient cohort [10]. However, the clinical efficacy rate is similar to that described in the previous cohort by Rebold et al. [10]. As we can see, all our patients had a Charlson Score of ≥ 3, which suggests that our patients had multiple comorbidities that increased their risk of mortality and complications, indicating a less favorable prognosis. Therefore, the excess deaths in our study could be related to the underlying chronic diseases of our patients rather than the infection itself.

Furthermore, clinical efficacy results are consistent with published clinical trials on treating carbapenem-resistant Gram-negative bacteria (CR-GNB) [11]. Recently, our group published a series of patients with CR-GNB infections, primarily *P. aeruginosa,* who were treated with FDC and demonstrated a higher rate of favorable clinical response [12]. However, clinical cure was defined as the resolution or improvement of signs and symptoms of infections. With similar definitions, the clinical cure rate might also be higher.

In our study, microbiological success was observed in 64.3%. These results could be justified by the difficulty of eradicating *P. aeruginosa*

Table 1 Description of the cohort with DTR-*Pseudomonas aeruginosa* infections treated with IMR

Case	Age (years), sex	Underlying disease	Charlson Score	Primary focus of infection	Procedure	Bacteremia	Sepsis/septic shock	Prior antibiotic therapy	Duration (days) of treatment with IMR	Adverse effect	Clinical efficacy	Microbiological efficacy	Mortality
#1	63, female	Solid cancer	4	Skin and soft tissue infection	No	Yes	Septic shock	COL, MER	30	No	No	No	Yes
#2	24, female	Cystic fibrosis	4	Lung infection (HAP)	No	No	Sepsis	MER, AMI	7	Nausea	Yes	Yes	No
#3	45, female	Klippel–Trénaunay syndrome	3	Skin and soft tissue infection	No	No	Sepsis	CAZ-AVI	21	No	Yes	Yes	Yes
#4	65, male	Solid cancer	3	Skin and soft tissue infection	Debridement	No	Sepsis	COL, MER	30	No	Yes	Yes	No
#5	70, male	Diabetes mellitus	7	Skin and soft tissue infection	Amputation	No	Septic shock	IMI	10	No	Yes	Yes	No
#6	72, male	COVID	4	Lung infection (VAP)	No	No	Sepsis	MER, CAZ-AVI	9	No	Yes	Yes	No
#7	61, male	Obesity	3	Skin and soft tissue infection	Amputation	No	Sepsis	P/T, GEN, CIP	10	No	Yes	Yes	No

Table 1 continued

Case	Age (years), sex	Underlying disease	Charlson Score	Primary focus of infection	Procedure	Bacteremia	Sepsis/septic shock	Prior antibiotic therapy	Duration (days) of treatment with IMR	Adverse effect	Clinical efficacy	Microbiological efficacy	Mortality
#8	73, male	No	3	Lung infection (VAP)	No	No	Septic shock	MER, CAZ-AVI, COL	4	No	No	No	Yes
#9	54, female	Solid cancer, COVID	4	Meningoventriculitis	External ventricular drainage	No	Septic shock	MER, CAZ-AVI	14	No	Yes	Yes	Yes
#10	50, male	Dyslipidemia,	3	Lung infection (VAP)	Pleural drainage	No	Septic shock	FEP, P/T, MER, LVX, C/T	14	No	Yes	Yes	No
#11	68, male	Acute necrotizing pancreatitis	3	Intraabdominal infection	Drainage of pancreatic abscesses	No	Septic shock	MER, CIP, AMI, COL, C/T	24	No	No	No	Yes
#12	75, female	Gonarthrosis	3	Skin and soft tissue infection	Debridement	Yes	Septic shock	FDC, C/T, CAZ-AVI MER, IMI, COL	10	No	No	No	Yes

Table 1 continued

Case	Age (years), sex	Underlying disease	Charlson Score	Primary focus of infection	Procedure	Bacteremia	Sepsis/septic shock	Prior antibiotic therapy	Duration (days) of treatment with IMR	Adverse effect	Clinical efficacy	Microbiological efficacy	Mortality
#13	50, male	No	3	Skin and soft tissue infection	Debridement	yes	Septic shock	P/T, FDC, MER, C/T, CAZ-AVI, CIP, COL	19	No	No	No	No
#14	42, female	No	3	Skin and soft tissue infection	Debridement	Yes	Septic shock	P/T, MEP, C/T	21	No	Yes	Yes	No

IMR imipenem/relebactam, *MER* meropenem, *CIP* ciprofloxacin, *LVX* levofloxacin, *FEP* cefepime, *P/T* piperacillin–tazobactam, *CAZ-AVI* ceftazidime/avibactam, *C/T* ceftolozane/tazobactam, *COL* colistin, *GEN* gentamicin, *AMI* amikacin, *FDC* cefiderocol, *VAP* ventilator-associated pneumonia, *HAP* hospital-acquired pneumonia, *NA* not available

Table 2 MICs (mg/l) and clinical categories of antimicrobial agents against the evaluated *P. aeruginosa* isolates

	P/T	CC	FEP	CC	CAZ	CC	CAZ/AVI	CC	C/T	CC	FDC	CC	IMI	CC	IMR	CC	MER	CC	MEV	CC	AZT	CC	CIP	CC	AMI	CC	TOB	CC	COL	CC
#1	32	R	8	I	16	R	ND	–	1	S	ND	–	≥ 16	R	ND	–	≥ 16	R	ND	–	≥ 64	R	0.5	I	4	(R)	≤ 1	(S)	≤ 0.5	S
#2	> 32/4	R	16	R	16	R	4/4	I	2/4	S	≤ 0.03	S	4	I	0,5/4	S	16	R	16/8	R	16	R	> 2	R	16	(S)	2	(S)	≤ 0.5	S
#3	> 64	R	> 16	R	> 16	R	16	R	ND	–	ND	–	> 8	R	ND	–	> 8	R	ND	–	> 16	R	> 2	R	> 32	(R)	8	(R)	≤ 2	S
#4	> 32/4	R	> 16	R	32	R	8/4	R	4/4	S	0.25	S	> 8	R	2/4	S	16	R	16/8	R	32	R	> 2	R	4	(S)	> 4	(R)	1	S
#5	> 32/4	R	> 16	R	> 32	R	16/4	R	8/4	R	0.5	S	> 8	R	2/4	S	16	R	16/8	R	> 32	R	> 2	R	16	(S)	2	(S)	2	S
#6	16/4	R	8	I	8	I	4/4	I	1/4	S	0.5	S	4	I	1/4	S	8	R	8/8	S	16	R	1	R	16	(S)	1	(S)	1	S
#7	> 32/4	R	> 16	R	> 32	R	> 16/4	R	8/4	R	4	R	8	R	2/4	S	16	R	16/8	R	> 32	R	2	R	16	(S)	1	(S)	1	S
#8	> 32/4	R	> 16	R	> 32	R	16/4	R	2/4	S	1	S	> 8	R	> 8/4	R	> 16	R	> 16/8	R	> 32	R	> 2	R	8	(S)	1	(S)	1	S
#9	32	R	32	R	16	R	16/4	R	2/4	S	1	S	64	R	4/4	R	128	R	ND	–	128	R	0.5	I	< = 8	(S)	< = 2	(S)	< = 2	S
#10	> 16	R	> 8	R	> 32	R	16	R	8	R	ND	–	> 4	R	ND	–	> 8	R	ND	–	ND	–	0.25	I	≤ 8	(S)	≤ 2	(S)	ND	–
#11	> 16	R	> 8	R	> 32	R	> 8	R	> 4	R	ND	–	> 32	R	ND	–	16	R	ND	–	ND	–	> 1	R	> 16	(R)	> 4	(R)	≤ 2	S
#12	> 16	R	> 8	R	32	R	24	R	12	R	ND	–	> 4	R	ND	–	> 8	R	ND	–	ND	–	> 1	R	≤ 8	(S)	≤ 2	(S)	≤ 2	S
#13	> 16	R	> 8	R	> 32	R	48	R	16	R	ND	–	> 4	R	ND	–	> 8	R	ND	–	ND	–	0.5	I	≤ 8	(S)	≤ 2	(S)	≤ 2	S
#14	> 32/4	R	> 16	R	> 32	R	16/4	R	4/4	S	0.125	S	> 8	R	4/4	R	16	R	16/8	R	> 32	R	≤ 0.5	I	8	(S)	≤ 0.5	(S)	2	S

P/T piperacillin-tazobactam, *CC* clinical category, *FEP* cefepime, *CAZ* ceftazidime, *CAZ-AVI* ceftazidime/avibactam, *C/T* ceftolozane/tazobactam, *FDC* cefiderocol, *IMI* imipenem, *IMR* imipenem/relebactam, *MER* meropenem, *MEV* meropenem–vaborbactam, *AZT* aztreonam, *CIP* ciprofloxacin, *AMI* amikacin, *TOB* tobramycin, *COL* colistin, Clinical categories are indicated between brackets, as indicated by EUCAST, *ND* MIC not determined

due to its high capacity for intrinsic, acquired, and adaptive resistance.

Diversifying antimicrobial treatment is essential to reducing antibiotic pressure and, in this way, reducing the risk of the emergence of resistant mutant strains. The emergence of resistance to IMR during treatment has recently been reported [13].

The limited sample size is a significant drawback of this study, constrained by the number of patients for whom compassionate use of this antimicrobial was requested at the national level for managing patients with confirmed DTR-*P. aeruginosa* infections. However, the strengths include strict definitions, a primary outcome such as mortality, and the scarcity of real-world data to date.

CONCLUSIONS

In conclusion, our study suggests that imipenem/cilastatin/relebactam may represent a treatment option for patients with DTR-*P. aeruginosa* infections, which should be validated in prospective clinical trials.

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Data Availability. All data generated or analyzed during this study are included within the article.

Declarations

Conflict of Interest. All named authors of this article confirm that they have nothing to declare.

Ethical Approval. The study was approved by the Ethics Committee (code 5317) of Reina Sofia University Hospital, Córdoba, Spain.

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