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BRIEF REPORT

Cefiderocol for the Treatment of Infections Due to Metallo-B-lactamase–Producing Pathogens in the CREDIBLE-CR and APEKS-NP Phase 3 Randomized Studies

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(See the Editorial Commentary by Marco Falcone and Giusy Tiseo on pages 1085–7.)

In the CREDIBLE-CR and APEKS-NP studies, cefiderocol treatment was effective against gram-negative bacteria producing metallo-B-lactamases; rates of clinical cure (70.8% [17/24]), microbiological eradication (58.3% [14/24]), and day 28 all-cause mortality (12.5% [3/24]) compared favorably with comparators of best-available therapy and high-dose meropenem (40.0% [4/10], 30.0% [3/10], and 50.0% [5/10], respectively).

Keywords. carbapenem resistance; cefiderocol; eradication; metallo-beta-lactamase; NDM.

A lack of effective therapies has led to a clear unmet need in the treatment of infections caused by gram-negative bacteria producing metallo-B-lactamases (MBLs) [1, 2], including imipenemase (IMP), Verona integron-encoded (VIM), and New-Delhi (NDM) MBLs, which confer carbapenem resistance (CR) [2]. NDM-producing CR Enterobacterales (CRE) infections are associated with unfavorable outcomes [3]. Additionally, MBL-producing CR *Pseudomonas aeruginosa* infections may be associated with a more rapid onset of illness and progression to death than non–MBL-producing *P. aeruginosa* infections [4]. Among the limited treatment options for MBL-producing pathogens [1], aztreonam plus ceftazidime-avibactam is considered effective, although the pharmacokinetics of the combination are not optimized [5]. Other antibiotics, such as polymyxins, fosfomycin, and tetracyclines, are active in vitro but may have poor efficacy [5].

Cefiderocol, a siderophore cephalosporin, is approved for the treatment of infections caused by MBL-producing CR pathogens [6]. It is stable against hydrolysis by IMP, VIM, and NDM MBLs [6].

We aimed to describe the outcomes of patients treated with cefiderocol for MBL infections in 2 recently completed phase 3, randomized, prospective clinical studies investigating the efficacy and safety of cefiderocol (CREDIBLE-CR and APEKS-NP) [7, 8].

METHODS

In the pathogen-focused, open-label, descriptive CREDIBLE-CR study (A Multi**C**enter, **R**andomiz**ED**, Open-label Cl**I**nical Study of S-649266 or **B**est Availab**LE** Therapy for the Treatment of Severe Infections Caused by **C**arbapenem-**R**esistant Gram-negative Pathogens; NCT02714595), cefiderocol (2 g, every 8 hours, or renal function–adjusted dosages) and best-available therapy (BAT; up to 3 gram-negative antibiotics dosed according to local practice) for 7–14 days were investigated in patients (N = 150; intention-to-treat/safety population) with serious CR infections [7].

In the double-blind, noninferiority *Acinetobacter*, *Pseudomonas*, *Escherichia coli*, *Klebsiella*, *Stenotrophomonas* - nosocomial pneumonia; NCT03032380 (APEKS-NP) study, critically ill patients with gram-negative nosocomial pneumonia (N = 298; intention-to-treat/safety population) received cefiderocol (2 g, every 8 hours infused over 3 hours, or renal function–adjusted doses) or high-dose, extended-infusion meropenem (2 g, every 8 hours, infused over 3 hours or renal function–adjusted doses) for 7–14 days [8]. As pathogen identification and susceptibility results were available following randomization, 59 patients were found to have meropenem-resistant isolates [8]. Physicians could either discontinue treatment if the pathogen was resistant to meropenem or continue treatment if patients had responded to therapy. Details of the study designs, outcomes, and molecular characterization of carbapenemases expressed in the baseline pathogens are described elsewhere [7, 8].

In the current report, patient-level information on MBL-producing bacterial infections is provided. Microbiological eradication at end of treatment (EOT), clinical cure at test of cure (TOC), and all-cause mortality (ACM) at day 28 are also summarized. Only descriptive statistical analyses were performed.

RESULTS

Across the 2 studies, 34 patients had an MBL-producing pathogen at randomization: 23 in CREDIBLE-CR (cefiderocol, 16; BAT, 7) and 11 in APEKS-NP (cefiderocol, 8; meropenem, 3) (Supplementary Tables 1 and 2). In total, 20 patients were infected with MBL-producing Enterobacterales and the

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remaining 14 patients were infected with non-fermenter species, such as *P. aeruginosa* or *Acinetobacter baumannii*. Patients were enrolled primarily in Europe and Asia (N = 30 centers). Most MBLs were NDM enzymes, which were expressed primarily in CREs (CREDIBLE-CR: 12/14; APEKS-NP: 6/6). Among non-fermenters, IMP, NDM, and VIM enzymes were detected. Across both treatment arms, cefiderocol minimum inhibitory concentrations (MICs) ranged from 0.12 to 32 μg/mL in the CREDIBLE-CR study and from 0.25 to 4 μg/mL in the APEKS-NP study.

In CREDIBLE-CR, the mean Acute Physiology and Chronic Health Evaluation II (APACHE II) score was similar between cefiderocol and BAT arms for patients with MBL infections. In APEKS-NP, the mean APACHE II score was lower in the cefiderocol than in the meropenem arm, but Sequential Organ Failure Assessment (SOFA) scores were similar (Supplementary Tables 1 and 2). Across studies, patients were generally younger in the cefiderocol arm than in the comparator arms. The proportion of males was 82.6% (19/23) in CREDIBLE-CR and 45.5% (5/11) in APEKS-NP.

In the CREDIBLE-CR study, most patients in the cefiderocol arm received monotherapy and only 3 had combination therapy with fosfomycin or piperacillin/tazobactam (Supplementary Table 1). Best-available therapy agents varied, including colistin-based therapy in 6 patients and amikacin plus doripenem in 1 patient. By protocol, all patients in APEKS-NP received cefiderocol or meropenem monotherapy. One of the 3 meropenem-treated patients discontinued the study drug due to resistance and received rescue therapy with colistin and fosfomycin.

In the CREDIBLE-CR study, clinical cure at TOC was numerically higher with cefiderocol (75.0% [12/16]) than with BAT (28.6% [2/7]), whereas in APEKS-NP, clinical cure rates were similar between cefiderocol (62.5% [5/8]) and meropenem (66.7% [2/3]) (Table 1). Microbiological eradication rates by EOT in the cefiderocol arm were 62.5% (10/16) in CREDIBLE-CR and 50.0% (4/8) in APEKS-NP, respectively. Eradication varied by diagnosis, presence or absence of NDM enzyme, or pathogen type in both studies (Table 1, Supplementary Tables 3 and 4). In CREDIBLE-CR, the eradication rate in the BAT arm by EOT was 14.3% (1/7) (Table 1, Supplementary Table 3); among NDM-producing pathogens, 70.0% (7/10) were eradicated in the cefiderocol arm compared with 0% (0/5) in the BAT arm. In APEKS-NP, the rates of cure at TOC and eradication at EOT in the meropenem arm were each 66.7% (2/3) (Table 1, Supplementary Table 4).

Across all MBL infections, there were numerical differences in clinical cure rates at TOC (cefiderocol, 70.8% [17/24]; comparators, 40.0% [4/10]) and eradication rates at EOT (cefiderocol, 58.3% [14/24]; comparators, 30.0% [3/10]) (Table 1). The numerical differences in clinical cure rates between cefiderocol and comparators were greater for infections caused by CRE than for infections caused by CR non-fermenters (Table 1).

Day 28 ACM rates with cefiderocol were numerically lower than with BAT in the CREDIBLE-CR study (cefiderocol, 6.3% [1/16]; BAT, 57.1% [4/7]), and similar between treatments in the APEKS-NP study (cefiderocol, 25.0% [2/8]; meropenem, 33.3% [1/3]). In CREDIBLE-CR, the only patient who died by day 28 had a CR *Enterobacter cloacae*–expressing NDM-1 and showed cefiderocol resistance at baseline (MIC = 16 μg/mL). Across studies, day 28 ACM was numerically lower among cefiderocol-treated patients (12.5% [3/24]) than comparator-treated patients (50.0% [5/10]). Mortality was not associated with infection type, MBL type, or type of pathogen (Table 1).

DISCUSSION

Cefiderocol, primarily administered as monotherapy, led to numerically higher clinical cure and microbiological eradication rates than comparators against MBL-producing pathogens, including both Enterobacterales and non-fermenters, in 2 randomized clinical studies that enrolled patients with nosocomial pneumonia, bloodstream infection/sepsis, or complicated urinary tract infections. Overall day 28 ACM was 12.5% [3/24] among cefiderocol-treated patients and 50.0% [5/10] for patients who received other agents. The benefit in outcomes was observed across different species and cefiderocol MIC values (ie, up to 4 μg/mL). Cefiderocol treatment showed effective eradication of bacteria with a high level of CR, as shown by meropenem and imipenem MIC values of 16 μg/mL or greater, and was apparent across different infection sites. The most frequent MBL was NDM (total of 22 of 34 patients), which was associated with cefiderocol MIC values of 4 μg/mL or less in 81.8% of cases (MIC = 4 μg/mL: n = 9; MIC <4 μg/mL: n = 9). Previously, in NDM-producing isolates, increased carbapenem and cefiderocol MICs have been observed [9]. To this end, cefiderocol susceptibility testing should be used to guide optimal treatment for infections caused by MBL-producing bacteria. Nonetheless, microbiological eradication and clinical cure rates were high among patients receiving cefiderocol who were infected with isolates displaying elevated MICs.

Cefiderocol or the combination of aztreonam with ceftazidime-avibactam has recently been recommended as potential treatment options for infections caused by MBL-producing CREs [10]. The combination of aztreonam with ceftazidime-avibactam has demonstrated in vitro synergism and low MIC values against CREs [5, 11]; however, higher MICs have been documented against MBL-positive *P. aeruginosa* [12]. In our investigation, cefiderocol MIC values for CR non-fermenters, mainly *P. aeruginosa*, ranged between 0.12 μg/mL and 4 μg/mL, and cefiderocol treatment afforded clinical benefit in MBL-producing CR *P. aeruginosa* infections. Taken together, cefiderocol appears to be effective as monotherapy against MBL-producing bacteria and offers an essential therapeutic option that does not require co-administration of 2 agents.

Table 1. Clinical Cure, Microbiological Eradication, and All-Cause Mortality at Day 28 in Infections Caused by Metallo-B-lactamase–Producing Bacteria in the CREDIBLE-CR and APEKS-NP Phase 3 Studies

	Clinical Cure at TOC		Eradication at EOT		ACM Day 28	
CREDIBLE-CR	Cefiderocol (N = 16)	BAT (N = 7)[a]	Cefiderocol (N = 16)	BAT (N = 7)[a]	Cefiderocol (N = 16)	BAT (N = 7)[a]
Overall	75.0 (12/16)	28.6 (2/7)	62.5 (10/16)	14.3 (1/7)	6.3 (1/16)	57.1 (4/7)
Types of infection						
Pneumonia	83.3 (5/6)	33.3 (1/3)	33.3 (2/6)	0 (0/3)	16.7 (1/6)	33.3 (1/3)
Other[b]	70.0 (7/10)	25.0 (1/4)	80.0 (8/10)	25.0 (1/4)	0 (0/10)	75.0 (3/4)
MBL type						
NDM	60.0 (6/10)	20.0 (1/5[a])	70.0 (7/10)	0 (0/5[a])	10.0 (1/10)	60.0 (3/5[a])
Non-NDM	100 (6/6)	33.3 (1/3[a])	50.0 (3/6)	33.3 (1/3[a])	0 (0/6)	33.3 (1/3[a])
Pathogen type						
Enterobacterales	80.0 (8/10)	0 (0/4)	70.0 (7/10)	0 (0/4)	10.0 (1/10)	75.0 (3/4)
Non-fermenters[c]	66.7 (4/6)	66.7 (2/3)	50.0 (3/6)	33.3 (1/3)	0 (0/6)	33.3 (1/3)
APEKS-NP	Cefiderocol (N = 8)	Meropenem (N = 3)	Cefiderocol (N = 8)	Meropenem (N = 3)	Cefiderocol (N = 8)	Meropenem (N = 3)
Overall	62.5 (5/8)	66.7 (2/3)	50.0 (4/8)	66.7 (2/3)	25.0 (2/8)	33.3 (1/3)
Type of infection						
Pneumonia	62.5 (5/8)	66.7 (2/3)	50.0 (4/8)	66.7 (2/3)	25.0 (2/8)	33.3 (1/3)
MBL type						
NDM	50.0 (3/6)	100 (1/1)	50.0 (3/6)	100 (1/1)	33.3 (2/6)	0 (0/1)
Non-NDM	100 (2/2)	50.0 (1/2)	50.0 (1/2)	50.0 (1/2)	0 (0/2)	50.0 (1/2)
Pathogen type						
Enterobacterales	60.0 (3/5)	100 (1/1)	60.0 (3/5)	100 (1/1)	20.0 (1/5)	0 (0/1)
Non-fermenters[d]	66.7 (2/3)	50.0 (1/2)	33.3 (1/3)	50.0 (1/2)	33.3 (1/3)	50.0 (1/2)
CREDIBLE-CR + APEKS-NP[e]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]	Cefiderocol (N = 24)	All Comparators[f] (N = 10)[a]
Overall	70.8 (17/24)	40.0 (4/10)	58.3 (14/24)	30.0 (3/10)	12.5 (3/24)	50.0 (5/10)
Type of infection						
Pneumonia	71.4 (10/14)	50.0 (3/6)	42.9 (6/14)	33.3 (2/6)	21.4 (3/14)	33.3 (2/6)
Other diagnoses[b]	70.0 (7/10)	25.0 (1/4)	80.0 (8/10)	25.0 (1/4)	0 (0/10)	75.0 (3/4)
MBL type						
NDM	56.3 (9/16)	33.3 (2/6[a])	62.5 (10/16)	16.7 (1/6[a])	18.8 (3/16)	50.0 (3/6[a])
Non-NDM	100 (8/8)	40.0 (2/5[a])	50.0 (4/8)	40.0 (2/5[a])	0 (0/8)	40.0 (2/5[a])
Pathogen type						
Enterobacterales	73.3 (11/15)	20.0 (1/5)	66.7 (10/15)	20.0 (1/5)	13.3 (2/15)	60.0 (3/5)
Non-fermenters	66.7 (6/9)	60.0 (3/5)	44.4 (4/9)	40.0 (2/5)	11.1 (1/9)	40.0 (2/5)

Data are presented as % (n/N) or % (n/N'), where N is the total number of patients in the treatment arm and N' is the total number of patients within the sub-category.

Abbreviations: ACM, all-cause mortality; APEKS-NP, Acinetobacter, Pseudomonas, Escherichia coli, Klebsiella, Stenotrophomonas - nosocomial pneumonia; BAT, best-available therapy; CREDIBLE-CR, A MultiCenter, RandomizED, Open-label CIInical Study of S-649266 or Best AvailabLE Therapy for the Treatment of Severe Infections Caused by Carbapenem-Resistant Gram-negative Pathogens; EOT, end of treatment; IMP, imipenemase metallo-B-lactamase; MBL, metallo-B-lactamase; NDM, New Delhi metallo-B-lactamase; TOC, test of cure.

[a]One isolate expressed an NDM and an IMP-62 MBL.

[b]Other infections: complicated urinary tract infection (cefiderocol: 6; BAT: 3), bloodstream infection/sepsis (cefiderocol: 4; BAT: 1).

[c]Cefiderocol: *Pseudomonas aeruginosa* (n = 4), *Acinetobacter baumannii* (n = 2); BAT: *P. aeruginosa* (n = 3).

[d]Cefiderocol: *P. aeruginosa* (n = 2), *A. baumannii* (n = 1); meropenem: *P. aeruginosa* (n = 2).

[e]No post hoc statistical analysis was planned; data are descriptive.

[f]All patients in the comparator arm of each study are included; comparators included treatments that were inactive in vitro based on susceptibility testing result (see Supplementary Tables 1 and 2).

Strengths of the current analysis include the powerful design of phase 3 clinical studies investigating cefiderocol, the real-world nature of the descriptive data provided (given the heterogeneity of the population), and the inclusion of diverse serious infections requiring intravenous antibiotic treatment. It is also notable that cefiderocol monotherapy was not confounded by potential activity of other agents. At randomization, 47.8% (CREDIBLE-CR) and 45.5% (APEKS-NP) of patients were in intensive care (Supplementary Tables 1 and 2), representing a population with severe disease. Further strengths are the range of CR pathogens and MBL enzymes demonstrating relatively higher cefiderocol MIC values, and the characterization of B-lactamase enzymes other than MBLs.

Limitations include the low number of patients, the lack of active comparator agents (in APEKS-NP), and the inability to analyze results by infection site. Stratification of patients based on baseline risk factors was not feasible in this post hoc analysis. Further, we did not evaluate resistance mechanisms such as porin mutations or efflux pump upregulation, which might have contributed to CR in *P. aeruginosa*, and consequently to outcomes. Additionally, the different study designs, comparator agents, and inclusion and exclusion criteria limit interpretation

of combined results. Finally, in MBL-producing CRE infections, mortality is associated with higher Charlson comorbidity index [4] and SOFA scores [5], despite administration of active agents. The impact of such factors in the current investigation, particularly given some numerical baseline inter-arm differences, cannot be discounted.

While further investigation is required to further define the role of cefiderocol in the treatment of MBL infections, our current investigation suggests that cefiderocol is a reasonable option for infections due to MBL-producing CREs and non-fermenters, supporting its recommendation in guidelines.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. All authors participated in the preparation of the manuscript.

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Potential conflicts of interest. Shionogi had a role in the design of the study, data acquisition, and analysis. J.-F. T. has received honoraria for participating in advisory boards for Pfizer, Merck, MedImmune, Paratek, Nabriva, Bayer, and Gilead, and for lectures for Pfizer, Merck, Biomérieux, Beckton-Dickinson, and Brahms; he has also received research grants from Merck, Pfizer, 3M, Beckton-Dickinson, and Gilead. M. P. is a consultant for Shionogi and has received investigator-initiated research funding. R. K. S. is a consultant for Shionogi, Merck, Venatorx, Pfizer, Menarini, and Melinta, and has received investigator-initiated research funding from Shionogi, Merck, Venatorx, and Melinta. T. B., S. P., and Y. Y. are employees of Shionogi. R. E. is a consultant for Shionogi and received consultancy fees. Y. Y. reports stocks from Shionogi & Co, Ltd.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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