

Update on antimicrobial pharmacotherapy

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Cefiderocol, a new antibiotic against multidrug-resistant Gram-negative bacteria

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ABSTRACT

Cefiderocol is a novel catechol-substituted siderophore cephalosporin that binds to the extracellular free iron, and uses the bacterial active iron transport channels to penetrate in the periplasmic space of Gram-negative bacteria (GNB). Cefiderocol overcomes many resistance mechanisms of these bacteria. Cefiderocol is approved for the treatment of complicated urinary tract infections, hospital-acquired bacterial pneumonia and ventilator-associated bacterial pneumonia in the case of adults with limited treatment options, based on the clinical data from the APEKS-cUTI, APEKS-NP and CREDIBLE-CR trials. In the CREDIBLE-CR trial, a higher all-cause mortality was observed in the group of patients who received cefiderocol, especially those with severe infections due to *Acinetobacter* spp. Further phase III clinical studies are necessary in order to evaluate cefiderocol's efficacy in the treatment of serious infections.

Keywords: Cefiderocol; multidrug-resistant Gram-negative bacteria; carbapenemases; extended-spectrum beta-lactamases

INTRODUCTION

Cefiderocol is a novel catechol-substituted siderophore cephalosporin, structurally similar to cefepime and ceftazidime [1,2]. Cefiderocol binds to the extracellular free iron, and uses the bacterial active iron transport channels to penetrate the outer cell membrane and enter the periplasmic space, overcoming many of the resistance mechanisms of Gram-negative bacteria (GNB), including efflux pump up-regulation and porin channel mutations [1]. Moreover, the side-chain properties

allow cefiderocol to remain highly stable against hydrolysis by various β -lactamases, including serine β -lactamases and metallo- β -lactamases [1]. In the periplasmic space, cefiderocol primarily binds to the penicillin-binding protein 3 (PBP3) and disrupts the cell wall synthesis, which results in the lysis and death of the bacteria. Cefiderocol also has affinity for PBP1a of *Pseudomonas aeruginosa* and PBP2 of *Klebsiella pneumoniae* [2]. Cefiderocol is highly active against a broad range of aerobic GNB, including carbapenem- and colistin-resistant bacteria, but has no activity against most Gram-positive bacteria and anaerobic bacteria [1]. It was approved by the Food and Drug Administration (FDA) in 2019 for the treatment of complicated urinary tract infections (cUTI), hospital-acquired bacterial pneumonia (HAP) and ventilator-associated bacterial pneumonia (VAP), and in 2020 by the European Medicines Agency (EMA) for the treatment of infections produced by aerobic GNB in adults with limited treatment options, after consultation with an infectious disease specialist.

CLINICAL EFFICACY TRIALS

Most experience with cefiderocol derives from clinical trials. The APEKS-cUTI trial (ClinicalTrials.gov, number NCT02321800) was a phase 2, multicentre, double-blind, parallel-group non-inferiority study performed at 67 hospitals in 15 countries, which enrolled patients with a clinical diagnosis of cUTI with or without pyelonephritis or those with acute uncomplicated pyelonephritis [3]. Patients were randomly assigned to receive 1 h intravenous infusions of cefiderocol (2 g) or imipenem-cilastatin (1 g each) every 8 h, for 7-14 days. Patients with an infection cause by a carbapenem-resistant bacterium were excluded. The primary endpoint was the composite of clinical and microbiological outcomes 7 days after the end of treatment. Between 2015 and 2016, 452 patients were randomly assigned to cefiderocol (303) or imipenem-cilastatin (149), of whom 448 patients (300 in the cefiderocol group and 148 in the imipenem-cilastatin group) received treatment.

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The most prevalent GNB isolated were *Escherichia coli* and *K. pneumoniae*. The primary efficacy endpoint was achieved by 73% of patients in the cefiderocol group and 55% of patients in the imipenem-cilastatin group, with an adjusted treatment difference of 18.58% (95% CI 8.23-28.92; $p=0.0004$), in favor of cefiderocol. No unexpected safety concerns were identified. The authors concluded that cefiderocol 2 g three times daily was non-inferior when compared to imipenem-cilastatin 1 g three times daily for the treatment of cUTI.

The randomized, double-blind, parallel-group, phase 3, non-inferiority trial APEKS-NP (ClinicalTrials.gov, NCT03032380), performed between 2017 and 2019 in 76 centers of 17 different countries, enrolled patients diagnosed with HAP, VAP, or health-care-associated Gram-negative pneumonia. The study randomly assigned 148 patients to receive a 3-h intravenous infusion of cefiderocol 2 g every 8 h and 152 participants to receive a 3-h intravenous infusion of meropenem 2 g every 8 h [4]. Treatment was usually prescribed for 7 to 14 days, but could be extended to 21 days based on the investigator's decision. Patients also received intravenous linezolid (600 mg every 12 h) for at least 5 days to ensure coverage of Gram-positive bacteria and of methicillin-resistant *Staphylococcus aureus*. The primary endpoint was all-cause mortality at day 14. *Klebsiella pneumoniae* (32%), *Pseudomonas aeruginosa* (16%), *Acinetobacter baumannii* (16%), and *Escherichia coli* (14%) were the most common GNB isolated, with extended-spectrum beta-lactamases (ESBL) frequently found in Enterobacteriaceae, and carbapenemases most common in *A. baumannii*. Out of 175 of patients, 60% were on mechanical ventilation, and 199 (68%) were admitted to the intensive care unit at randomization. All-cause mortality at day 14 was 12,4% with cefiderocol (18 out of 145 patients) and 11,6% with meropenem (17 out of 146 patients; adjusted treatment difference 0,8%, 95% CI 6,6-8,2; $p=0,002$ for non-inferiority hypothesis). The overall occurrences of treatment-emergent adverse events (TEAEs), drug-related TEAEs, serious adverse events, and TEAEs leading to study drug discontinuation were similar between treatment groups. The authors concluded that cefiderocol was non-inferior to high-dose, extended-infusion meropenem in patients with GNB nosocomial pneumonia (NP), and considered cefiderocol as a potential option for the treatment of patients with NP, including those caused by multidrug-resistant (MDR) GNB [4].

The CREDIBLE-CR study (ClinicalTrials.gov, NCT02714595) was a randomized, open-label, multicenter, parallel-group, pathogen-focused, descriptive, phase 3 study performed in 95 hospitals in 16 countries between 2016 and 2019 [5]. Patients diagnosed with NP, bloodstream infections (BSI) or sepsis, and cUTI, due to a carbapenem-resistant GNB were included. A total number of 101 patients were randomly assigned to receive a 3-h intravenous infusion of cefiderocol 2 g every 8 h (15% received one adjunctive antibiotic) while 49 were randomly assigned to receive the best available therapy, which was pre-specified by the investigator before randomization (61% received a combination therapy). Overall, 66% of patients who received cefiderocol reached clinical cure, compared to 58% of

patients treated with a combination of other antibiotics, while 48% treated with cefiderocol reached microbiological eradication compared to 26% in the comparator group [5]. Notwithstanding, the study raised some concerns as a higher proportion of patients treated with cefiderocol died by the end of the study (34% vs 18%, respectively). Most patients had received cefiderocol for a carbapenem-resistant *A. baumannii* infection (as a single bacteria or in combination with *P. aeruginosa* or *Stenotrophomonas maltophilia*). These results led the FDA to point out a potential reduction of cefiderocol's efficacy in patients with HAP, VAP and BSI, especially due a carbapenem-resistant *A. baumannii* [6].

The clinical trial GAME CHANGER (ClinicalTrials.gov, NCT03869437) is currently in progress. The study's primary outcome is to compare the 14-day mortality of a 2 g regimen of cefiderocol administered intravenously over 3 hours every 8 hours for a period of 7 to 14 days versus an antibiotic standard therapy for healthcare-associated and hospital acquired GNB BSI. The study is estimated to be completed in February 2022.

CONCLUSION

Cefiderocol is a novel cephalosporin with a promising activity against MDR GNB, including carbapenem-resistant GNB. It would be especially useful for the treatment of GNB with limited therapeutic options as those producing metallo- β -lactamases. Further evaluation in phase III clinical studies are necessary in order to evaluate its efficacy in the treatment of serious infections, especially those produced by carbapenem-resistant *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*.

CONFLICTS OF INTEREST

FLM has received fees from Shionogi for his participation as a medical advisor.

JTS presents no conflict of interest.

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