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Cefiderocol: A ray of hope for treatment of multidrug resistant gram negative bacteria

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Abstract
Cefiderocol is a novel, first in its class, siderophore antibacterial with activity against carbapenem-resistant gram-negative bacteria. Its unique structure and mechanism provide increased stability against beta lactamases. Presence of multi-drug resistance makes management of gram-negative infections difficult to treat due to the limited treatment options available. Cefiderocol has been approved by US Food and Drug Administration on 14 November 2019 for the treatment of patients 18 years of age or older with complicated urinary tract infections (cUTI), including kidney infections caused by susceptible Gram-negative microorganisms, who have limited or no alternative treatment options. The purpose of this article is to review data on the mechanism of action, pharmacokinetics, pharmacodynamics, efficacy, and safety of cefiderocol.

Keywords: Cefiderocol, complicated urinary tract infections (cUTI), Gram-negative bacteria, Multi drug resistance (MDR)

Introduction

Cefiderocol is a first in its class, an injectable siderophore antibacterial with activity against carbapenem-resistant gram-negative bacteria, including Enterobacteria [1] and nonfermenters [2]. Its novel bacterial cell wall penetration mechanism overcomes all classes of carbapenemases [3], porin channel mutations, and efflux pump overexpression [4]. Data on the clinical efficacy of cefiderocol are limited mainly to complicated urinary tract infections. Based on the results of a phase II trial [5], cefiderocol was granted US Food & Drug Administration (FDA) approval for the treatment of adult patients with complicated urinary tract infections (UTIs) caused by susceptible gram-negative bacteria with limited or no alternative treatment options in November 2019

The emergence of carbapenem resistance in Enterobacterales, Pseudomonas aeruginosa, and Acinetobacter baumannii is an urgent threat to global public health [6]. These Gram-negative organisms are common pathogens in a variety of serious infections, including intra-abdominal infections, pneumonia, urinary tract infections, and bloodstream infections (BSI) [7]. Because multi-drug resistance complicates the management of these infections due to the limited treatment options available. Previously, antibiotic options for multi-drug resistant (MDR) Gram-negative infections have included aminoglycosides, polymyxins, and/or tigecycline. These agents possess significant disadvantages, including toxicities, sub-optimal pharmacokinetics at target sites of infection, and poor outcome data [8]

Novel b-lactamase inhibitor combinations provide no clinically relevant protection for the parent b-lactam compound against other class D carbapenemases, such as OXA-23, OXA 40, OXA-51-like, which are the predominant enzymes driving carbapenem resistance in A. baumannii [9]. Also, non-b-lactamase-mediated mechanisms of resistance, such as mutations causing porin channel depletion or efflux pump upregulation, are becoming a growing threat in the development of carbapenem resistance, and the novel agents do not fully address this need [10, 11].

Cefiderocol is a new cephalosporin with potent in vitro activity against CRE and drugresistant non-fermenting Gram-negative bacilli. The purpose of this article is to review existing data on the mechanism of action, microbiology, pharmacokinetics, pharmacodynamics, efficacy and safety of cefiderocol.

Data Sources

Literature for this review was obtained through a search of Pubmed for all materials containing the name ‘‘cefiderocol’’. Additional sources were obtained through clinicaltrials.gov, FDA briefing document.

STRUCTURE

The chemical structure of cefiderocol contains a cephalosporin core with siderophore moeity. The aminothiazole ring and carboxypropyl-oxyimino group attached to the 7-position side chain confer enhanced activity against Gram-negative bacilli, including P. aeruginosa and A. baumannii. The combined structure of a cephalosporin and a siderophore moiety also confers enhanced stability against hydrolysis by many β-lactamases, including extended spectrum β-lactamases (ESBLs).

Mechanism of Action

Microorganisms require iron for important cellular redox processes. In order to survive under iron-depleted conditions in human hosts, pathogens possess various pathways for heme uptake and nonheme iron-acquisition mechanisms.[12] One such mechanism is the production and subsequent extracellular release of molecules called siderophores that scavenge for free ferric iron and undergo re-uptake into the cell as a siderophore–iron complex via iron transporter channels. Cefiderocol, a novel combination of a catechol-type siderophore and a cephalosporin antibiotic, utilizes the siderophore–iron complex pathway to penetrate the outer membrane of Gram-negative organisms in addition to normal passive diffusion through membrane porins. Once within the periplasmic space, cefiderocol dissociates from the iron and binds to penicillin-binding proteins (PBP), primarily PBP3, to inhibit peptidoglycan synthesis. This active transport mechanism also overcomes permeability-related drug resistance due to porin channel loss and overexpression of multidrug efflux pumps. [13, 14]

Spectrum and in Vitro Activity

Cefiderocol is approved for the treatment of severe pneumonia & cUTI caused by any of the following Gram-negative organisms: Acinetobacter baumannii complex, Escherichia coli, Enterobacter cloacae complex, Klebsiella pneumonia, Pseudomonas aeruginosa, Serratia marcescens.

Cefiderocol has potent in vitro activity against various lactose-fermenting enteric Gram-negative bacilli, including E. coli, Klebsiella spp., Enterobacter spp., Proteus spp., Providencia spp. Salmonella spp., Yersinia spp., and Vibrio spp., as well as non-fermenting organisms, such as Acinetobacter spp., Pseudomonas spp., Burkholderia spp., and Stenotrophomonas maltophilia. Cefiderocol has also demonstrated in vitro activity against Haemophilus spp., Moraxella catarrhalis, and Bordetella parapertussis, and the intrinsically multidrug-resistant Elizabethkingia meingoseptica. High minimum inhibitory concentrations (MICs) have been observed against most aerobic Gram-positive and anaerobic Gram-positive and Gram-negative organisms [15].

Pharmacokinetics

Cefiderocol follows linear pharmacokinetics, as examined in phase I and II studies. At steady-state, cefiderocol 2 g given as a 60-min infusion every 8 h in healthy adults achieved a peak serum concentration (Cmax) of 153 lg/mL, elimination half-life (t) of 2.72 h, and systemic clearance (Cl) of 3.89 L/h. Cefiderocol is predominantly excreted unchanged via the kidneys [16,17]. Cefiderocol was also examined in individuals with renal impairment (mild, moderate, or severe and end-stage renal disease (ESRD). Ratios of AUC in mild, moderate, severe renal impairment and ESRD compared to normal renal function were 1, 1.5, 2.5, and 4.1, respectively. This shows that cefiderocol exposure increases as renal function decreases. Plasma protein binding ranged from 53% to 65% [18]. In a population pharmacokinetic analysis of healthy patients and patients with complicated urinary tract infection (cUTI) cefiderocol pharmacokinetics were best described by a three-compartment model [17]. Effects of disease state on drug clearance and volume were observed with infected patients having 26% higher total clearance and 36% higher central compartment volume of distribution compared to healthy patients. Similar to other cephalosporins, the pharmacokinetic/pharmacodynamic index that best predicts activity is percentage of a 24-h time period that the unbound drug concentration exceeds the MIC (fT [MIC) [19–22]. Various dosing regimens were tested in murine thigh and lung infection models caused by Gram-negative bacteria, including E. coli, K. pneumonia etc. Mean % fT [MIC for a 1 log10 reduction was 73.3% for Enterobacterales models [22]. All dose-adjusted regimens for patients with renal impairment met these criteria.

The recommended dosage according to USFDA drug label is 2 grams administered every 8 hours by intravenous (IV) infusion over 3 hours in adults with a creatinine clearance (CLcr) of 60 to 119 mL/min. Dosage adjustment is recommended for patients with CLcr less than 60 mL/min or for patients with CLcr 120 mL/min or greater. The recommended duration of treatment is 7 to 14 days. The duration of therapy should be guided by the severity of infection and the patient’s clinical status for up to 14 days.

Further work is needed to assess intrapulmonary penetration in infected patients, mainly those who are critically ill. Drug–drug interaction potentials of cefiderocol were assessed in an open-label, randomized, crossover study of 3 study cohorts. Furosemide and metformin exposures were not impacted by cefiderocol co-administration [23].

Efficacy

The clinical efficacy of cefiderocol has been evaluated in a phase II study among adult patients with cUTI. This was a multicenter, double-blind, parallel-group, randomized, non-inferiority study comparing cefiderocol to imipenem/cilastatin. Adult patients with a diagnosis of cUTI were randomized 2:1 to receive cefiderocol 2 g every 8 h administered over 60 min or imipenem/cilastatin 1 g every 8 h for a duration of 7–14 days. The primary efficacy outcome was taken as a composite end point of clinical response and microbiological response at the test of cure assessment 5–9 days after the last dose of study medication. Response was evaluated in the modified intention-to-treat (mITT) population, which included all randomly assigned participants who received at least one dose of study drug. A total of 448 patients were randomized and received at least one dose of the study drug and 371 patients with a qualifying Gram-negative organism were included in the mITT population. Baseline demographics were comparable

between groups, with an average age of about 61 years and more than 50% female. Over 70% of patients in both arms had a diagnosis of cUTI with or without pyelonephritis, with E. coli being the most common pathogen isolated. The primary outcome of clinical and microbiological response was met in 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) of 119 patients in the imipenem/cilastatin group (adjusted treatment difference 18.58%; 95% CI 8.23–28.92; p = 0.0004) at test of cure. This met the pre-specified criterion for non-inferiority. At test of cure, microbiological response was higher in the cefiderocol group than the imipenem/cilastatin group (73% vs. 56%; 95% CI 6.92–27.58) with no differences in clinical response (90% vs. 87%; 95% CI - 4.66 to 9.44). This study was designed to demonstrate non-inferiority, but a post hoc analysis was consistent with superiority, with the adjusted treatment difference of 18.58% favoring cefiderocol and the lower limit of the CI exceeding zero. Treatment differences for patients with E. coli and K. pneumoniae were consistent with that in the mITT population. [24]. CREDIBLE-CR (NCT02714595) was a multicenter, randomized, open-label phase III study of cefiderocol compared to best available therapy (BAT) for the treatment of severe infections caused by carbapenem-resistant Gram-negative pathogens and was presented to the US FDA for drug approval . Patient included with diagnosis of healthcare-associated pneumonia (HCAP), hospital acquired pneumonia (HAP), ventilator associated pneumonia (VAP), cUTI and sepsis. Cefiderocol 2 g every 8 h was given as a 3-h infusion and BAT was chosen by the investigator and consisted of up to 3 antibacterials. The primary outcome was a clinical outcome at test of cure for patients with HAP/VAP/HCAP, sepsis, and a microbiologic outcome for patients with cUTI. A total of 101 patients were randomized to the cefiderocol arm and 49 patients to the BAT arm (safety population), with 80 and 38, respectively, having laboratory-confirmed infections of carbapenem-resistant Gram-negative bacilli. These 118 patients made up the CR-mITT population and were the primary efficacy population. Baseline demographics were comparable with a mean age of approx. 63 years. The most of the patients had a baseline diagnosis of pneumonia (44.6% cefiderocol vs. 44.9% BAT). While most patients in the cefiderocol arm received monotherapy (n = 66, 82.5%), the majority of patients in the BAT arm received combination therapy (n = 27, 71.1%), largely with colistin-based regimens. In the CR-mITT population clinical cure rates at test of cure were comparable between groups overall (52.5% cefiderocol vs. 50% BAT) and for each individual disease state HAP/VAP/HCAP (50% cefiderocol vs. 52.6% BAT), Sepsis (43.5% vs 42.9%), and cUTI (70.6% vs. 60%). However, all-cause mortality at day 14, day 28, and day 49 was, respectively, numerically higher in the cefiderocol group (18.8%, 24.8%, 33.7%) compared to BAT (12.2%, 18.4%, 20.4%). The hazards ratio for time to death with cefiderocol was 1.77, however the 95% confidence interval (0.87–3.57) crossed 1, with a p value of 0.11. [25]

APEKS-NP (NCT03032380) was a phase III, double-blind, randomized, active-controlled, non-inferiority trial of cefiderocol for the treatment of HAP, VAP, or HCAP caused by Gram negative pathogens. Patients were randomized to cefiderocol 2 g every 8 h or meropenem 2 g every 8 h, both as a 3-h infusion. Linezolid was administered in both arms for a duration of at least 5 days and cefiderocol or meropenem for 7–14 days [26]. The primary endpoint was all-cause mortality at day 14 in the modified intention-to-treat (ITT) population (ie, all patients receiving at least one dose of study drug, with a non-inferiority margin of 12.5%, excluding patients with Gram-positive monomicrobial infections. Cefiderocol was non-inferior with respect to all-cause mortality to meropenem at day 14 [12.4% vs. 11.6%] and day 28 [21.2% vs. 20.1%]. Mortality was also similar between groups at day 14, day 28, and end of study in the intention-to-treat population. Cefiderocol was shown to be non-inferior to high-dose, extended-infusion meropenem in terms of all-cause mortality on day 14 in patients with Gram-negative nosocomial pneumonia, with similar tolerability. The results suggest that cefiderocol is a potential option for the treatment of patients with nosocomial pneumonia, including those caused by multidrug-resistant Gram-negative bacteria. [25]

Case reports of clinical use of cefiderocol has also been documented.A 78-year-old female with extremely drug-resistant (XDR) P. aeruginosa native aortic valve endocarditis. This isolate was found to harbor a bla(Vietnam ESBL) gene and susceptible to only gentamicin, amikacin, and colistin. Despite combination therapy with colistin and gentamicin or colistin and meropenem, the patient was persistently bacteremic on days 56, 62, and 68, and the decision was made to request cefiderocol for compassionate use. Blood cultures cleared after 2 days of cefiderocol therapy, 1 day prior to valve surgery. Cefiderocol and colistin combination therapy was continued for an additional 3 weeks. An episodic transient neutropenia occurred at the end of therapy, but neutrophil counts returned to the normal range within a few days of stopping treatment [27]. Another case of 46-year-old patient with MDR P. aeruginosa intra-abdominal infection. After 28 days treatment of cefiderocol and metronidazole therapy, CT of the abdomen demonstrated complete resolution of the intra-abdominal abscess [28].

Safety

Based on phase I and phase II studies, cefiderocol is well tolerated and has a safety profile similar to that of other cephalosporins. In a phase I, dose-ascending study in 40 patients, no serious or clinically significant adverse events were observed. Cefiderocol was administered at doses of 100–2000 mg in the single-dose study and 1–2 g every 8 h in the multiple-dose study. In the single-dose study group, 9 adverse events were reported in 6/30 (20%) of patients with diarrhea (2 events in 2 subjects) and rash (2 events in 2 subjects) being the most common. In the 10-day multiple-dose study, 22 adverse events were reported by 16 subjects. These included alanine aminotransferase (ALT) level increase (n = 4), aspartate aminotransferase (AST) level increase (n = 4), creatine phosphokinase increase (n = 3), white blood cell increase (n = 2), rash (n = 2), and one case each of diarrhea, pyrexia, abdominal pain, headache, oropharyngeal pain, and urine positive for white blood cells. One participant in the multiple-dose group withdrew due to pyrexia [16]. In the other phase I trial, safety of cefiderocol was assessed in 30 participants with renal impairment. No serious adverse events or deaths were reported in this study. The most frequently reported adverse event was contact dermatitis (7.9%), which were assessed

as unrelated to the study drug. Drug-related adverse events were noted in 5 patients (13.2%), including nausea, maculopapular rash, urticaria, myalgia, and polyuria. There was no correlation between the incidence of adverse events and the degree of renal impairment. One patient discontinued treatment due to urticaria [18]. Adverse events in the phase II cUTI study were comparable between the cefiderocol and imipenem/cilastatin groups (41% vs. 51%). One death was reported in the cefiderocol group due to cardiac arrest, although this was considered unrelated to the study drug by the investigator [24]. The rate of adverse events in the phase 3 study were similar, with over 90% of patients in the cefiderocol arm and BAT arm experiencing at least 1 adverse event. The incidence of adverse events considered to be treatment-related were 14.9% in the cefiderocol arm and 22.4% in the BAT arm. The most common overall adverse events reported in the cefiderocol arm (C 10%) were diarrhea, increased ALT, increased AST, pleural effusion, and chest pain [25]. The effect of cefiderocol on QT was also evaluated in a phase I study in healthy adult subjects. Cefiderocol was given as a 3-h infusion in doses of 2 g, 3 g and 4 g compared to moxifloxacin 400 mg as control. No clinically significant effect was found on the QT interval or other ECG parameters with any cefiderocol dose. [29]. More studies will need to be conducted to assess drug–drug interactions.

Conclusion

Cefiderocol is a siderophore cephalosporin with broad spectrum of activity against serious infections caused by drug-resistant Gram-negative bacteria. Its mechanism of action which allows high intracellular penetration into the periplasmic space, favourable adverse event profile, low risk of drug interactions, and the ability to largely avoid all 3 mechanisms of carbapenem resistance in Gram-negative pathogens make cefiderocol an important antibiotic to have in our armamentarium. Cefiderocol has an important place in therapy for nosocomial pneumonia and cUTI, particularly in infections due to MDR Gram-negative organisms.

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