Clinical Infectious Diseases

SUPPLEMENT ARTICLE

Cefiderocol: A Novel Siderophore Cephalosporin Defeating Carbapenem-resistant Pathogens

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Cefiderocol, a novel siderophore cephalosporin in late-stage clinical development, utilizes a "Trojan horse" active transport mechanism to enter bacteria and has proven in vitro activity against carbapenem-resistant gram-negative pathogens, including those with major carbapenem-resistance mechanisms, and stability against all carbapenemases.

Keywords. cefiderocol; cephalosporin; carbapenem-resistant Enterobacteriaceae; nonfermenting gram-negative bacteria; siderophore.

The magnitude of carbapenem resistance in gram-negative bacteria has reached an alarming level globally [1, 2], increasing the risk of mortality and morbidity among vulnerable patient populations [3, 4].

The initial focus was on carbapenem-resistant Enterobacteriaceae (CRE) because of the rapid plasmid-mediated spread of carbapenemase enzymes (eg, New Delhi metallo-β-lactamase [NDM] or *Klebsiella pneumoniae* carbapenemase [KPC]) [5]; however, a large proportion of carbapenem-resistant infections are caused by nonfermenting gram-negative bacteria [6, 7] where resistance is both acquired or intrinsic and easily increased through porin loss and efflux pump activity [2, 8]. Recent data suggest that the rate of carbapenem resistance among nonfermenters has overtaken that of Enterobacteriaceae species, and represents a greater challenge for the treatment of severe infections such as nosocomial pneumonia or bacteremia in the United States [6] and Europe [7].

Thus, new agents with activity against all major mechanisms of carbapenem resistance are urgently needed [9, 10]. In recent years, several new antibiotics were approved; however, these new agents have a limited spectrum of activity, mainly toward the KPC-producing CREs, and resistance is already emerging [11–15].

This supplement to *Clinical Infectious Diseases* highlights the unique advantages of cefiderocol, a novel siderophore cephalosporin, and its role in the management of infections caused by carbapenem-resistant fermenters and nonfermenters. Cefiderocol (previously known as S-649266) is in late-stage clinical development by Shionogi & Co, Ltd, and was designed to overcome the challenges represented by all 3 major carbapenem resistance mechanisms [16]. Several other unique features can be attributed to its structural design including its stability against hydrolysis by all carbapenemases despite not being designed as a β-lactamase inhibitor [16]. Cefiderocol is a synthetic conjugate, with a cephalosporin moiety to inhibit cell wall synthesis and a siderophore moiety to gain entry into bacterial cells by active iron transporters, utilizing a "Trojan horse" approach, which is independent from porin channels and efflux pumps [15].

The first article by Nordmann and Poirel provides a comprehensive overview of the complexity of carbapenem resistance, including the different terminologies and the underlying molecular mechanisms, and the importance of rapid diagnostic tests to aid antibiotic selection for therapy [17]. The authors highlight the constantly changing epidemiology of CRE and carbapenem-resistant strains of the nonfermenters, such as *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, and *Stenotrophomonas maltophilia*. In the second article, Page elaborates on the role of siderophore molecules produced by bacteria and iron levels in hosts at the site of infection [18]. Siderophores are natural, small molecules that form a complex with iron, which is then actively transported into the bacterial cell via iron receptors. Development of synthetic siderophores conjugated with various antibiotics has been described by Page [18].

The article by Sato and Yamawaki describes the discovery and chemistry of cefiderocol, providing insights into the structure–activity relationship, the mechanism of action, the in vitro activity against carbapenem-resistant strains harboring certain resistance mechanisms, and the low potential of cefiderocol resistance [19]. The article also highlights the advantages of cefiderocol in comparison to previous siderophore antibiotics, including in vivo efficacy that correlates with its in vitro potency

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and a low potential of resistance development, paving the way for clinical investigations [19].

The in vitro potency of cefiderocol is discussed in detail by Yamano [20]. The ongoing global surveillance studies, SIDERO-WT and SIDERO-CR, periodically provide updates on the in vitro activity of cefiderocol compared with other β-lactam/cephalosporin antibiotics [21, 22]. These data demonstrated a very high rate of susceptibility to cefiderocol, importantly in *P. aeruginosa*, *A. baumannii*, and *S. maltophilia*. Supporting its high potency against a wide range of carbapenem-susceptible and -resistant pathogens, preclinical pharmacokinetic/pharmacodynamic (PK/PD) studies established that the PD driver of its efficacy is the fraction of time during which the concentration of cefiderocol remains above the minimum inhibitory concentration (*f*T/MIC), thereby establishing a target PD parameter of 75% *f*T > MIC as discussed in the article by Katsube et al [23]. In phase 1 clinical studies, a linear and predictable PK profile of cefiderocol was established, with minimal accumulation during multiple dosing, primarily renal clearance, and a low risk of drug–drug interactions [23]. The article by Echols et al presents an update on cefiderocol development, describing late-stage clinical trials for the treatment of patients with complicated urinary tract infection or acute pyelonephritis, nosocomial pneumonia, and bloodstream infections [24]. The "streamlined" clinical development program has addressed the regulatory requirements in both the United States and Europe to enable the approval of cefiderocol for the treatment of patients infected with carbapenem-resistant pathogens [24].

The final article by Doi provides an overview of the spectrum of activity, efficacy, and safety profile of the latest β-lactam–β-lactamase inhibitor combination drugs, and other recently approved agents such as eravacycline, plazomicin, and intravenous fosfomycin [25].

This supplement provides a summary of the development of the novel siderophore cephalosporin, cefiderocol. Its unique features and promising in vivo results suggest that cefiderocol has the potential to make an important contribution to the treatment of serious carbapenem-resistant gram-negative infections.

Notes

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