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Cefiderocol - a promising new antibiotic for the antibiotic-resistant pathogens of the highest epidemiological priority

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ABSTRACT:

Increase in the incidence of multidrug-resistant Gram-negative bacterial strains pose a significant threat to healthcare system worldwide. New antibiotics are necessary to combat particularly resitant pathogens. WHO's global priority pathogens list was published in 2017 to promote research and development of new antibiotics, as part of WHO's efforts to address growing global resistance to antimicrobial agents. Acinetobacter baumannii, Pseudomonas aeruginosa and carbapenem-resistant, third-generation cephalosporin-resistant Enterobacteriaceae were classified as highest priority pathogens requiring a new antibiotic treatment options. Cefiderocol is a novel parenteral siderophore cephalosporin that shows efficacy against listed Gram-negative bacteria. The results of the presented studies showed that cefiderocol has a strong antimicrobial effect against problematic strains that produce carbapenemases, such as KPC (K. pneumoniae carbapenemase) and B-class metallo-β-lactamases, including NDM-1 (New Delhi metallo-β-lactamase), as well as the

ESBL-producing strains. In addition, it does not require the use of the β-lactamase inhibitor. The new agent demonstrates a favorable side effect profile. There is an urgent need to develop new antibiotics. Cefiderocol is a new antibiotic that has a potential to effectively combat particularly resistant bacteries such as carbapenem-resistant Acinetobacter baumannii, Pseudomonas aeruginosa, as well as carbapenem and 3rd generation cephalosporin-resistant Enterobacteriaceae.

Key words: Cefiderocol; cephalosporin; antibiotic resistance

Introduction:

The emergence of multi-drug resistant bacterial pathogens has led to a global threat to public health, which is why, we urgently need new treatment options and drug delivery systems. Cefiderocol is a new siderophor cephalosporin, conjugated with a catechol residue at the third position side chain, recently developed, in order to control various bacterial pathogens, including those resistant to β-lactams and espiecially to the carbapenems. Gram-negative bacteria resistant to carbapenems are of utmost priority according to WHO [1]. Cefiderocol has broad activity against Enterobacteriaceae and non-fermenting bacteria such as Pseudomonas aeruginosa and Acinetobacter baumannii, including carbapenem-resistant strains. Cefiderocol primarily shows affinity for penicillin binding protein 3 (PBP3) of Enterobacteriaceae and non-fermenting bacteria, an essential protein of the divisome, activating peptide cross-linking between the glycan chains of the bacterial cell wall peptidoglycan.

The factors influencing the minimum inhibitory concentration (MIC) of cefiderocol were studied with different mutant strains. Deficiency of iron transporters PiuA in P. aeruginosa or both CirA and Flu in Escherichia coli caused a 16-fold increase in MICs of cefiderocol, suggesting that these transporters assist with outer membrane transfer of the drug. Deficiency of OmpK35/36 in Klebsiella pneumoniae, a group of outer membrane porins, which made the strain more susceptible to some β-lactams, and overproduction of efflux pump MexAB-OprM in P. aeruginosa demostrated no significant effect on the potentil activity of cefiderocol [2].

Acinetobacter baumannii is an important non-fermenting species of Gram-negative bacteria, which shows a large increase in resistance to carbapenems. The resistance has developed by the acquisition of exogenous enzymes, activation of efflux pump and a deficiency of channels porins or by activation or an additional acquisition of OXA-type enzymes [3,4,5]. Pseudomonas aeruginosa has a significant resistance, either endogenous or exogenous, caused by an overproduction of a large number of efflux pumps, overproduction of chromosomal β-lactamase AmpC, recovery of exogenous metalo-β-lactamases (MBL) and the porinal OprD deficiency [8,9,10]. Stenotrophomonas maltophilia is also an important hospital pathogen, naturally resistant to many antibiotics and disinfectants, often with a high degree of resistance due to various mechanisms, such as reduced permeability, β-lactamases, aminoglycoside-modifying enzymes and efflux pumps. [11,12]

The aim of the work is a presentation of a potential new drug for multi-resistant Gram-negative bacterial strains.

A review of available research:

In vitro activity of Cefiderocol (S-649266) was evaluated in non-fermenting Gram-negative bacteria A. baumannii, P. aeruginosa and S. maltophilia, including defined drug-resistant strains. Cefiderocol was synthesized in Shionogi & Co., Ltd. (Osaka, Japan). Two types of global collection of clinical isolates of A. baumannii, P. aeruginosa and S. maltophilia were used in these studies, which were collected by two internationally recognized microbiological facilities: International Health Management Associates, Inc. (Schaumburg, IL, USA) and JMI Laboratories (North Liberty, IA, USA). One was a set of randomly collected clinical isolates from the period 2009-2011, including 104 isolates of A. baumannii, 104 isolates of P. aeruginosa and 108 isolates of S. maltophilia. Another set was a collection of strains resistant to β-lactams collected in 2000-2009, including 99 strains of A. baumannii and 103 strains P. aeruginosa. A. baumannii strains were resistant to carbapenems (29), resistant to ceftazidime (20), resistant to colistine (10) and MDR strains (30). P. aeruginosa strains were resistant to carbapenems (10), resistant to ceftazidime (20), MBL (33) and MDR (30). The activity of S-649266 was compared with the activity of meropenem, levofloxacin, cefepime, ceftazidime and piperacillin/tazobactam. The MICs of the compounds were determined by microdilution on the medium.The obtained results indicate that S-649266 has a stronger in vitro activity against non-fermenting Gram-negative bacteria with significantly lower MIC90 values, compared to ceftazidime, meropenem, levofloxacin, cefepime and piperacillin/tazobactam [13].

In the study conducted by Akinobu Ito et al. the in vitro activity of cefiderecol against Pseudomonas aeruginosa was increased in iron-depleted conditions. This study explains the basic mechanisms responsible for the strong in vitro activity of cefiderocol against P. aeruginosa. Cefiderocol showed a strong activity of the siderophore, and the catechol residue on the side chain contributed to iron chelating activity. Due to its catechol group, cefiderocol was more efficiently transported to bacterial cells under iron-free conditions than under conditions sufficient iron supply, resulting in increased in vitro activity against P. aeruginosa. Based on the results of the study, conclusions were drawn: the in vitro antibacterial activity of cefiderocol is increased in iron depleted media, and the catechol residue is important for the antimicrobial activity of ceflerocol. This study proves that cefiderocol uses the P. aeruginosa own iron transport system to reach its site of action. Catechol part of the agent binds extracellular iron, imitating the siderofor proteins of this bacterium. It has been shown that the antibacterial activity of cefiderocol as well as uptake by P. aeruginosa cells is influenced by the iron concentration in the medium, which is consistent with the fact that the expression of outer membrane protein (IROMP) is increased under conditions of iron depletion [14].

Naoki Kohira et al. investigated the antimicrobial activity of S-649266 against various clinical isolates of Enterobacteriaceae, including those producing carbapenemase. Two sets of strain collections, a total of 850 clinical isolates of Enterobacteriaceae, were used to assess the antimicrobial activity of cefiderocol. The first set consisted of 617 clinical isolates obtained from various regions, including North America, Europe, Africa, Asia, Latin America, the South Pacific and the Middle East. It consisted of 106 E. coli isolates, 105 K. pneumoniae isolates, 103 Serratia marcescens isolates, 100 Citrobacter freundii isolates, 100 isolates of Enterobacter aerogenes and 103 isolates of Enterobacter cloacae. The second set included 233 strains that were obtained from various regions, including North America, Europe, Asia Pacific, and Latin America. These strains were characterized by resistance to various β-lactam

antibiotics with specific mechanisms associated with the production of ESBL (extended spectrum β-lactamase) of class A, type OXA beta-lactamase or various types of carbapenemases. The results showed that with regard to the characterized β-lactamase producing strains, S-649266 has a strong antimicrobial effect against problematic strains that produce carbapenemases, such as KPC (K. Pneumoniae carbapenemase) and class B metallo-β-lactamases, including NDM-1 (New Delhi metallo-β-lactamase), as well as ESBL producing strains. Cefiderocol does not require augmentation with the use of a β-lactamase inhibitor. S-649266 is fairly stable against various β-lactamases, including ESBL and class B carbapenemases (NDM-1, VIM and IMP) and class A (KPC, NMC and SME) [15].

The in vitro activity of cefiderocol, ceftazidime/avibactam, ceftolozane/tazobactam and other related drugs against imipenem resistant Pseudomonas aeruginosa, imipenem resistant Acinetobacter baumannii and Stenotrophomonas maltophilia was examined. Non-duplicated bacterial isolates resistant to imipenem P. aeruginosa, resistant to imipenem A. baumannii and S. maltophilia were analyzed. Impenem resistant P. aeruginosa strains and imipenem resistant A. baumannii strains were defined as isolates showing a MIC of ≥8 mg/L of imipenem. MIC of cefiderocol was ≤4 mg/L for five isolates of resistant to colistin and imipenem P. aeruginosa and 70% of 10 resistant to imipenem A. baumannii strains. Cefiderocol showed stronger in vitro activity than ceftolozane/tazobactam and ceftazidime/ avibactam against imipenem-resistant P. aeruginosa strains, imipenem-resistant A. baumannii and S. maltophilia. [16]

Akinobu Ito et al. in additional evaluation determined the effect of chromosomal overproduction of AmpC on the in vitro activity of cefiderocol and MIC for isogenic mutant strains of P. aeruginosa PAO1. The chromosomal cephalosporinase AmpC is a type of mechanism of cephalosporin resistance that occurs with expposure to β-lactam antibiotics. AmpC enzymes are inducible and can be expressed at high levels due to strain mutations. Overexpression can result in a resistance to broad-spectrum antibiotics. This is due to the inactivation of genes that regulate AmpC expression such as ampD and dacB. The MICs of ceftazidime and cefepime for PAO1 were increased 4- to 16-fold by inactivation of ampD and dacB, whereas inactivations had little effect for cefiderocol (≤2-fold increase for ampD or dacB). Inactivation of the ampC gene on the MIC of the cefiderocol as well as ceftazidime and had a limited effect (decrease ≤2-fold), in contrast to the imipenem, which showed an 8-fold decrease in MIC. These results suggest that the antimicrobial activity of ceftazidime, cefepime and imipenem are reduced by induced AmpC levels, while cefiderocol action is not. Similar results were presented for mutants overproducing AmpC, isolated from clinical isolates of P. aeruginosa and E. cloacae. The difference between the cefiderocol MIC values for the parental strains and their derivatives was ≤4-fold (P. aeruginosa SR24 and E. cloacae 1480700). On the other hand, the MIC values for ceftazidime, cefepime and aztreonam for Ampc producing isolates were 16 times or more than 16 times higher than for parental strains. Cefiderocol showed in vitro activity against AmpC overproducing strains, low affinity to chromosomal AmpC β-lactamases and low tendency to induce AmpC β-lactamases of P. aeruginosa and E. cloacae over time. This may explain the strong antimicrobial activity of cefiderocol against drug-resistant AmpC β-lactamase producing strains. [17]

A study conducted at DaVita Clinical Research in Minneapolis, Minnesota and Lakewood, Colorado, evaluated the pharmacokinetics and safety of cefiderocol in subjects with impaired renal function. The results were assessed after a single 1000mg, intravenous, 1-hour infusion of cefiderocol. Individuals with mild, moderate or severe and end-stage renal

failure requiring hemodialysis were compared demographically (age, sex and body mass index) with matched healthy subjects with normal renal function. The hemodialysis effect on cefiderocol clearance was also evaluated. The total plasma clearance and terminal plasma half-life correlated with renal function. The maximum plasma concentration was similar between the groups with impaired renal function and the group with normal renal function. About 60% of cefiderocol were removed by hemodialysis within 3 to 4 hours. The unbound to plasma proteins fraction was similar in studied groups regardless of renal function. The occurrence of adverse events does not seem to have any correlation with the degree of renal failure. Single intravenous doses of 1000 mg of cefiderocol were generally well tolerated in patients with renal impairment, with the exception of 1 patient, who had to had an infusion discontinued, due to development of urticaria. Renal insufficiency affected the area under the curve of concentration versus time, total clearance, and half-life, without affecting the maximum concentration. Cefiderocol has been significantly removed by sequential hemodialysis. The results of this study suggest the need to adjust the dose of ceflerocol based on renal function in patients with moderate and severe renal impairment and patients with end-stage renal disease and the need for an additional dose in patients undergoing hemodialysis [18].

James A.Karlowsky et al. determined the in vitro susceptibility of the collection from 2000-2016 consisted of 8 954 Gram-negative bacteria isolates, provided by 100 clinical laboratories in North America and Europe on cefiderocol using clinical and laboratory standards with the microdilution method. To test ceflerocol, Mueller-Hinton agar with reduced iron content was used. The concentration of cefiderol inhibiting 90% isolates (MIC90) was 0.5/L (North America, n=2470) and 1 mg/L (Europe; n=3543) for Enterobacteriaceae, 0.5 (North America; n=619) and 0.5mg/L (Europe; n=921) for Pseudomonas aeruginosa, 1 (North America, n=308) and 2mg/L (Europe; n=664) for Acinetobacter spp., 0.5 (America North; n= 165) and 0.25 mg/L (Europe; n=175) for Stenotrophomonas maltophilia and 0.12 (North America; n=40) and 0.5 mg/L (Europe; n=49) for Burkholderia cepacia complex spp. MIC of cefiderocol was <4 mg/L for 99,9% (6005/ 6013) Enterobacteriaceae, 99,9% (1539/1540) P. aeruginosa, 96,4% (937/972) Acinetobacter spp., 99.4% (338/340) S. maltophilia and 94.4% (84/89) of Burkholderia cepacia complex spp. For the meropenem-insensitive isolates, the MIC values for cefiderocol were ≤ 4 m/L for 99.6% (245/246) Enterobacteriaceae, 99.7% (394/395) P. aeruginosa, 96.1% (540/562) of Acinetobacter spp., and 87.1% (27/31) of B. cepacia complex spp. The results suggest that cefiderocol showed strong in vitro activity (MIC, ≤4 mg/L) in the vast majority (99.4%, 8 903/8,954) of clinical isolates of Gram-negative bacteria in a multi-continental collection from 2000-2016, including those insensitive to carbapenems. Additionally no cross resistance between cefiderocol and colistin was observed [19].

The collection of carbapentem-resistant gram-negative bacteria isolated from clinical specimens in 18 Greek hospitals has been tested for susceptibility to cefiderocol, meropenem, ceftazidime, cefepime, ceftazidime / avibactam, ceftolozane / tazobactam, aztreonam, amikacin, ciprofloxacin, colistin and tigecycline. The MIC method was determined by microdilution. A total of 189 non-fermenting Gram-negative bacteria (107 Acinetobacter baumannii and 82 Pseudomonas aeruginosa) and 282 Enterobacteriaceae (including 244 Klebsiella pneumoniae, 14 Enterobacter cloacae and 11 Providencia stuartii) were examined. In the case of both A. baumannii and P. aeruginosa, the MIC90 value of cefiderocol was 0.5 mg/L. For K. pneumoniae, E. cloacae and P. stuartii, the MIC90 of cefiderocol was 1,1 and

0.5 mg/L, respectively. Tigecycline was the second most active antibiotic, and the third most active antibiotic was colistin. [20]

Sean M. Stainton et al. evaluated the stability of humanized cefiderocol exposures in vivo over 72 hours to pathogens with MICs for cefiderocol of 0.5-16 μg/ml in the mouse model. With Acinetobacter baumannii, Pseudomonas aeruginosa and Enterobacteriaceae showing MIC values of 0.5-8 (n=11), enduring bactericidal activity was observed after 72 hours among 9 isolates. The MIC values after exposure revealed a single increase in two dilutions compared to the control in one animal (1/54 sample, 1.8%) after 72 hours. Adaptive resistance was not observed during therapy [21].

Simon Portsmouthet al. evaluated the efficacy and safety of cefiderocol against imipenem-cilastatin in the treatment of complicated urinary tract infection in patients at risk of contracting multi-drug resistant Gram-negative bacteria. A second-phase, multicenter, double-blind trial was conducted for parallel groups in 67 hospitals in 15 countries. Adults (≥ 18 years old) admitted to the hospital with a clinical diagnosis of complicated urinary tract infections with or without pyelonephritis or those with acute uncomplicated pyelonephritis were randomly assigned for intravenous, 1-hour infusions of cefiderocol (2g) or imipenem-cilastatin (1g each) three times a day, every 8 hours for 7-14 days. Patients were excluded if they had an initial urine culture with more than two uropathogens, urinary tract infections or pathogens known to be resistant to carbapenems. 452 patients were randomly assigned to cefiderocol (n=303) or imipenem-cilastatin (n=149), of whom 448 patients (n=300 in the cefiderocol group, n=148 in the imipenem-cilastatin group) received treatment. 371 patients (n=252 patients in the cefiderocol group, n=119 patients in the imipenem-cilastatin group) had a Gram-negative uropathogen and were included in the basic efficacy analysis. The primary efficacy endpoint was achieved in 183 (73%) of 252 patients in the cefiderocol group and 65 (55%) from 119 patients in the imipenem-cilastatin group (p=0.0004), determining the effectiveness of cefiderocol. Cefiderocol was generally well tolerated. Side effects occurred in 122 (41%) of 300 patients in the cefiderocol group and 76 (51%) of 148 patients from the imipenem-cilastatin group, with gastrointestinal disorders (i.e. abdominal pain, nausea, diarrhea, constipation, and vomiting) as the most common adverse reactions in both treatment groups (35 [12%] patients in the cefiderocol and 27 [18%] patients in the imipenem-cilastatin group). The intravenous infusion of cefiderocol was no-inferior than that of imipenem-cilastatin in the treatment of complicated urinary tract infection in people with multi-drug resistant Gram-negative bacteria [22].

Conclusions:

Cefiderocol offers a new promising treatment option against multi-drug resistant strains of Gram-negative pathogens. Numerous studies confirm its stable pharmacokinetics properties and efficacy against wide range of β-lactamases. The drug is currently in phase II of clinical trials and the preliminary results are very promising.

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