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Fetroja® (cefiderocol): A Modern Day Trojan Horse of Urinary Tract Infections

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Urinary tract infections (UTI) are among the most common community and hospital-acquired bacterial infections.[1] Additionally, according to the CDC, catheter-associated UTIs are the most common hospital care-acquired infection reported to the National Healthcare Safety Network (NHSN).[1] Due to human female anatomy, the shorter urethra allows for easier migration of bacteria to the bladder, which is reflected by the higher prevalence of UTIs in females with up to 60% having at least one UTI in their life.[2,3] UTIs can be defined as cystitis or pyelonephritis depending on site and extent of infection.2 These infections can be further stratified into complicated or uncomplicated infections.[2] According to the American Urological Association (AUA), an uncomplicated UTI is defined as a UTI in a healthy patient without anatomical or functional abnormalities and no known factors making the patient susceptible to develop a UTI.4 The AUA defines a complicated UTI (cUTI) as a UTI in a patient that has one or more complicating factors increasing the risk for developing a UTI and decreasing efficacy of therapy.[4] These complicating factors include: anatomic or functional abnormality of the urinary tract, an immunocompromised host, and a multi-drug resistant pathogen.[4] Other sources include additional factors such as: male sex, elderly, hospital-acquired infection, pregnancy, indwelling urinary catheter, recent urinary tract intervention, recent antimicrobial use, symptoms greater than seven days at presentation, diabetes mellitus, renal failure, renal transplant, poorly controlled diabetes and immunosuppression.[1,5]

Uropathogens, typically from the gut, may colonize the urethra and migrate to the bladder via flagella or pili where they can multiply to significant numbers causing cystitis.[1,2] These uropathogens may continue to ascend to the kidneys via the ureters and result in pyelonephritis.[1,2] Typical causative organisms include gram-negative bacteria such as Enterobacteriaceae, with Escherichia coli being the most common.1 However, gram-positive bacteria, such as Enterococcus spp., and fungal pathogens, such as Candida spp., may be seen as well especially in the setting of a cUTI.[1,6]

A positive urinalysis demonstrating pyuria, bacteria, or presence of nitrites can aid in the diagnosis of UTI, but the presence of symptoms is the main reason for diagnosis.[1] In the absence of symptoms, asymptomatic bacteriuria is considered and is generally not treated except in specific patient populations such as pregnancy.[1,4] Symptoms of cystitis include dysuria, urinary frequency or urgency, and/or suprapubic pain.[7] Additional systemic symptoms like fever or chills, flank pain, costovertebral tenderness, or altered mental status are suggestive of infection that has spread beyond the bladder and pyelonephritis should be present.[7] Urine cultures, ideally obtained prior to empiric therapy, demonstrating numbers of a uropathogen above a given threshold aids in the diagnosis and treatment of UTIs.[1,2,4] Imaging is recommended in those who are severely ill, have persistent symptoms after 48 to 72 hours of appropriate antimicrobial therapy, or have suspected urinary tract obstruction.[4,8]

As gram-negative bacteria are the most common pathogens in UTIs, antibiotics with gram-negative coverage are recommended for empiric therapy.[1,8] Selection of antibiotics and duration of therapy depend on type of diagnosis (cystitis vs pyelonephritis), complication (complicated vs uncomplicated), and severity of the infection.[4] In the setting of cystitis, narrow-spectrum antibiotics which concentrate in the urine are preferred agents.[1,8] These agents would include nitrofurantoin, fosfomycin, and trimethoprim/sulfamethoxazole (TMP/SMX) for empiric therapy.8 Of these agents, nitrofurantoin and fosfomycin exhibit minimal resistance and minimal propensity for collateral damage.[8] TMP/SMX is an appropriate choice, given local resistance rates of uropathogens do not exceed 20%, due to demonstrated efficacy in numerous clinical trials.8 Duration of therapy ranges from one to five days for cystitis and can be extended based on physician clinical judgement.[1,8]

In the setting of pyelonephritis, antibiotics that achieve high serum and renal tissue concentrations are preferred due to the infection being spread beyond the bladder and into the upper urinary tract.[1] For this reason, agents such as nitrofurantoin and fosfomycin are not recommended because of poor penetration outside of the bladder.[1] Empiric agents for the treatment of pyelonephritis include TMP/SMX, fluoroquinolones, aminoglycosides, and β-lactams.[1,8] Duration of therapy ranges 5- 14 days for pyelonephritis.[1,8] Parenteral agents are typically reserved for those with

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severe infections, such as those hemodynamically unstable, whereas, oral agents are preferred in less severe patients and can generally be treated outpatient.[1] Once susceptibility data is obtained, empiric antibiotic therapy should be de-escalated and more targeted to help reduce further antibiotic resistance and medication burden.

Fetroja® (cefiderocol) is a cephalosporin antibacterial that has received approval from the U.S. Food and Drug Administration (FDA) for the treatment of cUTIs (with or without pyelonephritis) and acute uncomplicated pyelonephritis.[9] Cefiderocol is approved in those infections caused by E. coli, K. pneumoniae, P. mirabilis, and E. cloacae complex in those 18 years of age or older with limited or no alternative treatment options based on positive results from a phase II study.[9] This medication provides a unique way to circumvent antibiotic resistance mechanisms continually growing in today's society. The purpose of this article is to assess the safety and efficacy of cefiderocol for the treatment of UTIs.

Clinical Pharmacology

Mechanism of Action

Structurally, cefiderocol is a hybrid of ceftazidime and cefepime, which are third and fourth generation cephalosporins, respectively.[10] Cefiderocol is a fourth-generation siderophore cephalosporin that has been shown to promote the formation of chelated complexes with ferric iron and facilitate active transport across the outer membrane of gram-negative bacilli via the iron transport system (sometimes termed the "Trojan horse strategy").[10] Once inside the bacteria, cefiderocol binds to penicillin binding proteins (PBPs), mainly PBP3, thereby inhibiting peptidoglycan synthesis resulting in cell death.[10]

Pharmacokinetics

Peak concentrations of cefiderocol after 2 g IV every eight hours in those with creatinine clearance (CrCL) >60 mL/min and diagnosed cUTI was 138 mg/mL.11 In healthy volunteers, a single 2 g dose administered over three hours resulted in a Cmax of 89.7 mg/mL.11 Cefiderocol experiences 40% to 60% protein binding, mainly to albumin.[11] Cefiderocol is minimally metabolized, primarily excreted through the kidneys with 60% to 90% unchanged in urine, and has a mean half-life of 2.0 to 2.7 hours.[11-13]

Pharmacodynamics

Similar to other cephalosporins, cefiderocol exhibits bactericidal activity.[10] Cefiderocol demonstrates time-dependent killing against Enterobacteriaceae, P. aeruginosa, A. baumannii, and S. maltophilia.11 Three-hour infusions increased percent time of dosing interval over the minimum inhibitory concentration (MIC) compared to one-hour infusions.[11] There are also no reports of clinically relevant QT-prolongation at one to two times the maximum recommended dosage (2 g every eight hours).[11]

Table 1 | Select Cefiderocol Pharmacokinetics[11-13]

Absorption	
C_{max}[a]	89.7-138 mg/mL
Distribution	
Vd[b]	18 L (±3.36 L)
Protein Binding	40-60% (Albumin)
Metabolism	
Minimal (<10%)	
Elimination	
Cl[c]	4.6-6.0 L/h L/hr
T1/2[d]	2.0-2.7 hours
Fecal Excretion	2.8%
Renal Excretion	98.6%

[a]Maximum plasma concentration; [b]Volume of distribution; [c]Clearance; [d]Half-life

Clinical Trials

Phase II Trial

There is currently one published phase II clinical trial comparing safety and efficacy of cefiderocol to imipenem-cilastatin in UTIs. Portsmouth et al. conducted a phase II, multicenter, double-blind, parallel-group non-inferiority trial that took place at 67 hospitals in 15 countries.14 This study included patients 18 years or older with a clinical diagnosis of cUTI with or without pyelonephritis (defined as inflammation of the renal pelvis and kidneys) or acute uncomplicated pyelonephritis. Patients with cUTI met the FDA clinical diagnostic criteria: clinical syndrome identified by pyuria and documented or suspected microbial pathogens on urine or blood cultures, in combination with local and systemic signs and symptoms of infection (fever, chills, malaise, flank pain, back pain, or costovertebral angle pain or tenderness) occurring in the presence of an anatomical or functional abnormality or catheterization, and requiring intravenous therapy.[14,15] The enrollment of patients with diagnosed acute uncomplicated pyelonephritis was limited to 30%, therefore leaving a majority of the studied population with cUTI. Patients were excluded if they had more than two uropathogens at a baseline urine culture, a fungal UTI, pathogens known to be resistant to carbapenems, or a CrCL of less than 20 mL/min.

Participants were randomized in a 2:1 ratio to receive either IV cefiderocol or IV imipenem-cilastatin and stratified by clinical diagnosis (cUTI with or without pyelonephritis or acute uncomplicated pyelonephritis). Participants received one-hour infusions of either cefiderocol (2 g) or imipenem-cilastatin (1 g) every eight hours for seven to 14 days. Doses were adjusted based on renal function, body weight, or both. Clinical and microbial response was assessed at different timeframes: day four (±1 day; early assessment), last day of study drug (end of treatment), seven days (±2 days) after end of treatment (test of cure), and about 14 days after end of treatment (follow-up).[14] Safety was assessed daily and at each timeframe in every patient who received at least one dose of study drug. Both groups followed a modified intention-to-treat (ITT) protocol which included patients who received at least one dose of study drug and had qualifying gram-negative uropathogens defined as $\geq 1 \times 10^5$ CFU/mL.

The primary endpoint was the composite of clinical and microbiological response at the test of cure assessment. The secondary endpoints were safety, clinical and microbiological response at early assessment, end of treatment, and follow-up, clinical and microbiological response per-pathogen and per-patient at early assessment, end of treatment, test of cure, and follow-up. Investigators evaluated clinical response based on the patient's signs and symptoms and defined response as resolution or improvement in symptoms present at study entry and with an absence of new symptoms.[14] Microbiological response was based on urine cultures with response defined as 1x104 CFU/mL or less.[14] Safety was

Table 2 | Microbiological Response[14]

	Cefiderocol (n=252)	Imipenem-cilastatin (n=119)	Treatment difference, % (95% CI)
Early Assessment			
Microbiological Eradication	232 (92%)	108 (91%)	1.28 (-4.83 to 7.39)
Microbiological Failure	14 (6%)	7 (6%)	-
Indeterminate	6 (2%)	4 (3%)	-
End of Treatment			
Microbiological Eradication	244 (97%)	114 (96%)	1.10 (-3.04 to 5.25)
Microbiological Failure	3 (1%)	3 (3%)	-
Indeterminate	5 (2%)	2 (2%)	-
Test of Cure			
Microbiological Eradication	184 (73%)	67 (56%)	17.25 (6.92 to 27.58)
Microbiological Failure	53 (21%)	44 (37%)	-
Indeterminate	15 (6%)	8 (7%)	-
Follow-up			
Sustained Microbiological Eradication	144 (57%)	52 (44%)	13.92 (3.21 to 24.63)
Microbiological Failure	84 (33%)	42 (35%	-
Indeterminate	24 (10%)	25 (21%)	-

assessed by identification of adverse events, measurements of vital signs, clinical laboratory tests (blood chemistry, hematology, and urinalysis), and electrocardiography (ECG).[14]

Of the 448 patients treated, 300 received cefiderocol and 148 received imipenem-cilastatin. The modified ITT population was comprised of 371 patients (cefiderocol n=252, imipenem-cilastatin n=119) who met criteria which was utilized for the primary efficacy analysis. Baseline characteristics were similar between the two treatment groups and included E. coli (cefiderocol group: 60.3% vs imipenem-cilastatin group: 66.4%) and K. pneumoniae (cefiderocol group: 19.0% vs imipenem-cilastatin group: 21.0%) as the most prevalent uropathogens in both groups. Resistance rates of cefepime, levofloxacin, and imipenem for E. coli and K. pneumoniae isolates were also similar between both groups. Both groups had a higher proportion of patients with pyelonephritis (any type) compared to cUTI without pyelonephritis (cefiderocol: 52% vs 48%; imipenem-cilastatin: 54% vs 46%).

The primary efficacy endpoint was achieved in 183 (73%) patients in the cefiderocol group and 65 (55%) in the imipenem-cilastatin group at test of cure (seven days ±2 days after end of treatment) with an adjusted treatment difference of 18.58% (95% CI [8.23 to 28.92]; p=0.0004). The proportion of patients who achieved a clinical response was similar at the test of cure assessment between the cefiderocol group and imipenem-cilastatin group (90% vs 87%) with a treatment difference of 2.39% (95% CI [-4.66 to 9.44]). The proportion of patients who achieved a microbiological response at the test of cure assessment was statistically different between groups with higher rates in the cefiderocol group (73%) compared to the imipenem-cilastatin group (56%) with a treatment difference of 17.25% (95% CI [6.92 to 27.58]). A subgroup analysis based on clinical diagnosis, sex, and age showed consistent results compared to the modified ITT population, favoring the cefiderocol group. Median duration of treatment was similar between groups at 9.0 days (SD 2.7) for the cefiderocol group and 9.0 days (SD 2.0) for the imipenem-cilastatin group. Despite favorability of cefiderocol in the overall modified ITT population, the composite of clinical and microbiological response was primarily driven by the microbiological response.

In the cefiderocol group, 122 of 300 patients (41%) and 76 of 148 patients (51%) of the imipenem-cilastatin group experienced adverse events with the majority being mild or moderate in severity. The most common adverse events reported were gastrointestinal disorders including diarrhea (4% vs 6%) and constipation (3% vs 4%). In the cefiderocol group, 14 of 300 patients (5%) and 12 of 148 patients (8%) in the imipenem-cilastatin group experienced serious adverse events. C. difficile colitis was the most common serious adverse event reported. There was one death reported due to cardiac arrest in the cefiderocol group, but the patient involved had a complicated medical history and the death was considered unrelated to the medication.

The investigators conducted a post-hoc analysis to assess superiority of cefiderocol vs imipenem-cilastatin. This analysis demonstrated favorability towards cefiderocol mainly due to higher eradication of gram-negative pathogens by the cefiderocol group at the test of cure assessment. Due to similar resistance rates of pathogens between groups, this difference was not due to resistance to imipenem.

Phase III Trial

Bassetti et al. conducted a prospective, international, multicenter, open-label, parallel-group, randomized, phase III clinical trial known as the CREDIBLE-CR study.[16] Currently, results have yet to be fully published, but limited data is available. CREDIBLE-CR compared cefiderocol to best available therapy (BAT) in patients 18 years or older with clinically diagnosed hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), healthcare-associated pneumonia (HCAP), bloodstream infections (BSI) or sepsis, or cUTI caused by carbapenem-resistant (CR) gram-negative bacteria. Patients in the cefiderocol group received cefiderocol 2 g infused over three hours every eight hours for seven to 14 days. The BAT group received up to three antibiotics in combination for seven to 14 days. Duration of therapy could be extended up to 21 days at the discretion of the investigators.

Table 3 | Clinical Response[14]

	Cefiderocol (n=252)	Imipenem-cilastatin (n=119)	Treatment difference, % (95% CI)
Early Assessment			
Clinical Eradication	228 (90%)	108 (91%)	-0.26 (-6.57 to 6.05)
Clinical Failure	23 (9%)	10 (8%)	-
Indeterminate	1 (<1%)	1 (1%)	-
End of Treatment			
Clinical Eradication	247 (98%)	118 (99%)	-1.07 (-3.42 to 1.29)
Clinical Failure	4 (2%)	0	-
Indeterminate	1 (<1%)	1 (1%)	-
Test of Cure			
Clinical Eradication	226 (90%)	104 (87%)	2.39 (-4.66 to 9.44)
Clinical Failure	14 (6%)	8 (7%)	-
Indeterminate	12 (5%)	7 (6%)	-
Follow-up			
Sustained Clinical Eradication	205 (81%)	86 (72%)	9.02 (-0.37 to 18.41)
Clinical Failure	19 (8%)	13 (11%)	-
Clinical Relapse	12 (5%)	12 (10%)	-
Indeterminate	16 (6%)	8 (7%)	-

Despite broadening inclusion criteria to include several types of bacterial infections, this study was not powered to detect statistically significant differences in the primary endpoint (clinical cure rates at the test of cure assessment in those with HAP/VAP/HCAP or BSI/sepsis caused by CR gram-negative pathogens and microbiological outcome at the test of cure assessment in those with cUTI caused by CR gram-negative pathogens). Although the study was underpowered, the 28-day all-cause mortality was higher in the cefiderocol group compared to the BAT group (25/101 (24.8%) vs 9/49 (18.4%)) and remained elevated at day 49 (34/101 (33.7%) vs 10/49 (20.4%)).[14,16]

Adverse Effects and Precautions

The most common adverse events reported are infusion reactions, rash, nausea, vomiting, diarrhea, constipation, hypokalemia, increased liver function test, headache, and candidiasis.[11] Serious adverse events include hypersensitivity reactions and Clostridium difficile associated diarrhea (CDAD). Precautions include history of seizures, due to the propensity for cephalosporins to cause seizures, and development of drug-resistant bacteria.[11] Additionally, the FDA approved labelling includes a warning for increase in all-cause mortality based on the phase III CREDIBLE-CR open-label trial. Although rare, discontinuation of cefiderocol therapy due to adverse reaction is most commonly due to diarrhea, drug hypersensitivity, or increased hepatic enzymes.[11]

Dosing and Administration

Cefiderocol is currently only indicated for the treatment of cUTI with or without pyelonephritis and acute uncomplicated pyelonephritis in those 18 years or older.[11] The dosing for both indications is the same and is typically 2 g infused over three hours every eight hours. There are dose adjustments based on renal function with adjustments at CrCL >120 mL/min, 30 to 59 mL/min, 15 to 29 mL/min, and <15 mL/min. Those renal dose adjustment that are all infused over three hours are 2 g every six hours, 1.5 g every eight hours, 1 g every eight hours, and 0.75 g every 12 hours, respectively.[11] Patients on hemodialysis may receive 0.75 g infused over three hours every 12 hours after hemodialysis as cefiderocol is removed during hemodialysis.[11] After reconstitution, Fetroja® (cefiderocol) can be stored for up to one hour at room temperature or up to four hours at room temperature once diluted in the infusion bag.[11]

Cost and Availability

Cefiderocol is sold under the brand name Fetroja® and manufactured by Shionogi & Co., Ltd. Currently, the only product on the market is 1g reconstitutable vials for intravenous use at the cost of $220 per vial.[17] Based on the duration of therapy per FDA approved labeling, the cost of a typical course of therapy (seven to 14 days) would range around $9,240 to $18,480 for the Fetroja® alone. There is no information regarding coverage through third-party claims.

Clinical Implications

Although there are encouraging results based on the APEKS-cUTI study, several limitations exist which may hinder cefiderocol's use in practice. The goal of therapy in cUTIs is cure and the APEKS-cUTI study demonstrated a statistically significant difference in the primary outcome. Microbiological response was the primary driver of the primary outcome. Despite a statistically significant difference in microbiological response in favor of cefiderocol, no difference in clinical response was seen. Considering the complexity of the patient population included in the study, they are at increased risk of treatment failure and may benefit from repeat urine cultures.[18] The results of the APEKS-cUTI

study demonstrate cefiderocol is at least non-inferior to imipenem -cilastatin and possibly superior at least regarding microbial eradication. Additionally, the APEKS-cUTI study only included patients 18 years or older. UTIs are not specific to a certain age group, but they can occur at any age.[19] Given that women are affected more often than men, another consideration is the possibility of pregnancy. Although pregnancy is typically excluded in clinical trials due to ethical concerns, the APEKS-cUTI study had a higher proportion of women than men and most participants were ≥65 years old. Given that being elderly is one criterion for a cUTI which is seen in the general population, this study included what would typically be seen in practice.[1,5] This allows for better generalizability to the average patient population considering prevalence of UTI increases with age as seen with a prevalence of about 20% in women 65 years of age or older compared to 11% in the overall population.[19] Since the investigators wanted to capture a more complicated patient population, a limit of 30% was set because patients with acute uncomplicated pyelonephritis tend to be young, healthy women without anatomical or functional abnormalities and have infections cause by susceptible pathogens.[14]

The APEKS-cUTI study also excluded patients with a CrCL <20 mL/min, but the Fetroja® package insert includes a dose adjustment for patients with a CrCL <15 mL/min.11 Although the approval of cefiderocol was preceded by the APEKS-cUTI study, the renal dose adjustment recommended in to package insert is based on a pharmacokinetic study demonstrating an increased area under the curve (AUC) in patients with a CrCL <15 mL/min.[11] Not only did the trial that got cefiderocol approved not include patients with a CrCL <20 mL/min, the pharmacokinetic study only included six patients in the CrCL <15 mL/min group.[11] Considering cefiderocol is a hybrid of ceftazidime and cefepime, which both require renal dose adjustments, it is likely cefiderocol may need dose adjustments for those with a CrCL <20 mL/min.10 With participants stratified to cUTI with pyelonephritis versus without pyelonephritis, more participants in both groups did not have pyelonephritis. However, when comparing proportion of participants with cUTI without pyelonephritis to those with pyelonephritis (any type), the majority of participants had pyelonephritis (any type). The authors did not conduct statistical analyses to determine if these baseline characteristics were statistically significant. Although not one of the objectives of the APEKS-cUTI study, there is uncertainty of the effect that a higher proportion of pyelonephritis versus cystitis included in the study had on the outcome, if any.

Considering complete results of the CREDIBLE-CR study have yet to been published, information should be extrapolated, if at all, with caution. Additionally, the study was not powered to detect a statistically significant difference in the primary outcome. However, preliminary results of an increase in all-cause mortality in the cefiderocol group has led to the inclusion of a warning in the package insert of an increase in all-cause mortality. Although the cause of the increased all-cause mortality is yet to be confirmed, the patients included in the CREDIBLE-CR study were already at increased risk of mortality simply due to the severity of their disease. The patients included in the trial were those with evidence of a CR gram-negative infection, which alone has an attributable mortality rate of between 26% – 44%.20 This was not seen in the APEKS-cUTI study due to exclusion of CR-organisms. Despite both groups in the CREDIBLE-CR study including similar patients, the cefiderocol group experienced higher mortality. Although this difference between groups could have been due to chance alone, this potential adverse event is a large risk. Given the weight that a finding of increased mortality holds, future studies should include mortality in the outcomes to aid in assessing cause or disproving this finding. Unlike the APEKS-cUTI study, CREDIBLE-CR utilized BAT which was the standard of care for CR infections at each site.16 Despite being underpowered, CREDIBLE-CR may provide hopeful results to guide future studies to assessing cefiderocol effectiveness versus the standard of care.

Table 4 | Adverse Drug Reactions[11]

Dermatologic	Infusion reaction (4%), Rash (3%)
Endocrine	Hypokalemia (2%)
Gastrointestinal	Diarrhea (4%), Constipation (3%), Nausea (2%), Vomiting (2%), C. difficile colitis (<1%)
Hepatic	Increased liver function test (2%)
Neurologic	Headache (2%)
Immunologic	Hypersensitivity reaction (<2%)
Other	Candidiasis (2%), Death

Both studies utilized active comparators with imipenem-cilastatin in the APEKS-cUTI study and BAT in the CREDIBLE-CR study. Although imipenem-cilastatin is an agent that can be used in cUTIs, carbapenems are not first line agents because they are broad spectrum antibiotics and can promote development of multi-drug resistant (MDR) organisms if used frequently.[18] For this reason, carbapenems like imipenem-cilastatin are reserved for cases of MDR infections.[1,18] Considering the CREDIBLE-CR study utilized standard of care, this allows assessment of how effective cefiderocol is compared to therapy typically seen in practice. However, by including BAT as the comparator in the CREDIBLE-CR study, cefiderocol was not compared to another last-line agent, but rather, possibly first-line agents. The most common pathogens were included in APEKS-cUTI and CREDIBLE-CR, but there are other pathogens that may be seen in practice in these disease states, such as gram-positive pathogens. At least in regard to infections caused by Enterococcus spp., cefiderocol will likely have no effect due to the intrinsic resistance to cephalosporins by these organisms.[21] This leaves it unclear as to what role, if any, cefiderocol has in those types of infections. With the many current available treatment options for cUTI with or without pyelonephritis and acute uncomplicated pyelonephritis, it is uncertain if cefiderocol will make its way into more common use other than its current indication. With the steep price of a full course of therapy with cefiderocol, much less expensive alternatives exist that can be utilized instead given the pathogen is susceptible. The similarity of adverse events and the increased rate of all-cause mortality (if truly caused by cefiderocol) further decreases its utility.

Based on current data of cefiderocol, it seems its use is limited to situations with little or no options available. Given the narrower spectrum of activity, cefiderocol may be used as a carbapenem-sparing therapy, but additional studies are required to further assess its use. Although the Trojan horse strategy that cefiderocol provides brings a novel approach to combatting bacterial pathogens, data is currently lacking to support its use in patients other than those with limited or no therapeutic alternatives. Furthermore, cefiderocol was approved based on one phase II trial. Considering the purpose of a phase II trial is to assess whether or not the medication works for the specific disease state

as well as safety in those patients, the trial is in a small sample size especially in relation to the prevalence of UTI reported by the CDC. The FDA may have preemptively approved cefiderocol due to the growing need for new antibiotics to combat the growing MDR organisms. Having been approved based on a single phase II trial, and that trial having its own limitations, considerable information is missing. Additional prospective, multi-center, phase III trials should be conducted aiming to further assess cefiderocol safety and efficacy. These studies should also assess renal dose adjustments including patients with CrCL <20 mL/min. Resistance rates and how quickly pathogens become resistant to cefiderocol are also unclear and may only be seen if cefiderocol becomes more widely used.

Conclusion

Fetroja® (cefiderocol) is a new siderophore cephalosporin that achieved FDA approval in November 2019 for the treatment of complicated urinary tract infections in adults 18 years and older who have limited or no alternative treatment options. Despite the warning of increased all-cause mortality included in the labeling of Fetroja® (cefiderocol), the APEKS-cUTI trial demonstrates its safety and efficacy. Given its high cost of therapy, similar side effect profile to currently available antibiotics, and its potential for increased mortality, it seems cefiderocol's place in therapy is in those with limited or no other options. Additional studies are warranted to establish safety and efficacy in other types of infections caused by multi-drug resistant pathogens especially as a carbapenem-sparing therapy.

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Personalized Medicine Corner

Pharmacogenetics of NSAIDS and CYP2C9

Amanda Elchynski, PharmD

Background

Patients with variants in the CYP2C9 gene who were to take select nonsteroidal anti-inflammatory drugs (NSAIDs), such as celecoxib, meloxicam, and ibuprofen would have increased concentration of the active drug. This increased concentration was proposed to place patients with this variant at an increased risk of developing adverse events.

Patient Case

JR is a 52 yo male with arthritis who presents to his primary care physician for a follow-up. JR would like to start a medication to help with his pain. After a discussion with the physician, and the goals of therapy, the physician, decided an NSAID would be most appropriate. The physician would like to prescribe celecoxib. The physician scans the medical chart to determine if the patient has any contraindications and sees the patient has "Encounter for pharmacogenetic testing" in his problem list. Under the problem, it directed the provider to see the encounter note that was placed three months ago. When entering into the pharmacogenetic encounter, the physician notices a table with information on CYP2C9 and the relationship with NSAIDs .

What is CYP2C9?

CYP2C9 is a drug-metabolizing enzyme encoded by a highly polymorphic gene; variants confer alleles that are either decreased or non-functional and are assigned a particular activity value (e.g., 0 and 0.5). Individuals have two alleles, which make up their genotype; the sum of the activity values from each allele makes up their activity score, which is used to translate to phenotype. Individuals may have one of three phenotypes; poor metabolizer (activity score of 0 or 0.5; little to no enzyme activity), intermediate metabolizers (activity score of 1 or 1.5; little enzyme activity), or normal metabolizer (activity score of 2; normal enzyme activity). For example, patient JR's genotype is CYP2C9 *2/*3; this is translated below.

Pharmacogenetic Test Results

CYP2C9 Genotype= *2/*3
*2 Activity value= 0.5
*3 Activity value =0
Genotype-based Activity Score = 0.5
Phenotype= Poor Metabolizer

What is the relationship between NSAIDs and CYP2C9?

Select NSAIDs (i.e., celecoxib, flurbiprofen, ibuprofen, meloxicam, and piroxicam) undergo inactivation by CYP2C9; variability in CYP2C9 can impact the exposure the patient has to the active drug. Patients who have increased exposure to the active drug are at increased risk of adverse events such as myocardial infarction and upper gastrointestinal bleeding. This risk of adverse events applies to all patients using NSAIDS, no matter the duration (i.e., chronically, short-term, and PRN). Adverse events from NSAIDs are dose-related, and there is strong evidence showing a pharmacokinetic difference among CYP2C9 phenotypes, which is how the Clinical Pharmacogenetics Implementation Consortium (CPIC) came up with dosing recommendations. However, to note at this time, there is limited evidence comparing the pharmacokinetic data to the outcome of adverse events.

Drug Therapy Recommendations for JR

Patients who are CYP2C9 poor metabolizers have prolonged half-life of celecoxib, and higher concentrations, which may increase JR's risk of adverse events. Based on these results, celecoxib should be initiated at 25-50% of the lowest recommended starting dose (50 mg BID). Titrate up to clinical effect or 25-50% of the max recommended dose. Titration should not occur for at least eight days, which will allow celecoxib to reach steady state. Alternatively, consider NSAIDs that do not have evidence of CYP2C9 impacting their metabolisms, such as aspirin or sulindac.

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