Efficacy of Fosfomycin for Injection vs Piperacillin-Tazobactam in Adults With Complicated Urinary Tract Infection and Acute Pyelonephritis: ZEUS Study Outcomes in Patients With Reduced Study Drug Susceptibility or Clinical Relapse at Late Follow-Up

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INTRODUCTION & PURPOSE

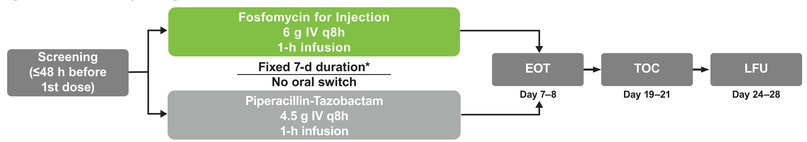
- Complicated urinary tract infections (cUTIs) typically develop in patients with structural or functional abnormalities of the urinary tract or in individuals with significant medical or surgical comorbidities[1]
- cUTIs are associated with substantial healthcare costs and compared with uncomplicated UTIs, a greater prevalence of drug-resistant pathogens[1]
- The increasing global rate of antibiotic resistance, including in multidrug resistant gram-negative uropathogens, has created a need for safe and effective antimicrobials with differentiated mechanisms of action[2,3]
- Fosfomycin for injection (FOS) is an injectable epoxide antibiotic with a broad spectrum of in vitro activity, including against multidrug-resistant gram-negative bacteria, and a unique mode of action that involves inhibiting an early step in bacterial cell wall synthesis[4,5]
- FOS is being pursued for US registration for the treatment of cUTI and acute pyelonephritis (AP), and safety and efficacy of FOS vs piperacillin-tazobactam (PIP-TAZ) were demonstrated in the phase 2/3 ZEUS trial in hospitalized adults with cUTI/AP[6]
- Although FOS resistance has been observed in several in vitro studies, resistance rates in clinical settings have remained relatively stable despite >40 years of clinical use of FOS outside of the United States[7]
- Here we report outcomes in patients who (a) developed reduced susceptibility to FOS or PIP-TAZ after enrollment in ZEUS and (b) experienced clinical relapse at late follow-up (LFU)

METHODS

- ZEUS was a multicenter, double-blind, phase 2/3 noninferiority trial in hospitalized patients aged ≥18 years with suspected or microbiologically confirmed cUTI/AP[6] **(Figure 1)**
  - ≥30% of patients were to have a diagnosis of AP at study entry
- Patients were randomized 1:1 to receive 6 g intravenous (IV) FOS every 8 hours (q8h) or 4.5 g IV PIP-TAZ q8h for 7 days
  - Patients with baseline bacteremia received ≤14 days of treatment
  - Oral step-down therapy was prohibited
- The primary outcome was overall success (clinical cure and microbiologic eradication) in the microbiologic modified intent-to-treat (m-MITT) population at the test-of-cure (TOC) visit (Day 19–21)
  - Clinical cure was assessed by the investigator and was defined as complete resolution or significant improvement of baseline signs and symptoms of cUTI or AP such that no further antimicrobial therapy was warranted
  - Microbiologic eradication was achieved if the baseline bacterial pathogen(s) were reduced to <10[4] colony-forming units (CFU)/mL on urine culture, or if repeat baseline-positive blood cultures were negative
    - Microbiologic outcomes were redefined post hoc using pulsed-field gel electrophoresis (PFGE) typing, whereby microbiologic persistence required the same genus and species of baseline and postbaseline pathogens as well as PFGE-confirmed genetic identity
  - The m-MITT population included all randomized patients who received any amount of study drug and at baseline had ≥1 gram-negative pathogen from an appropriately collected pretreatment baseline urine or blood sample
- Secondary outcomes included clinical cure, sustained clinical cure (defined as meeting clinical cure at TOC and remaining free of cUTI or AP signs and symptoms at LFU [Day 24–28]), and microbiologic persistence (defined as the urine culture at Day 5, end of treatment [EOT; Day 7–8], or TOC growing ≥10[4] CFU/mL for any of the baseline pathogen[s] identified at study entry and/or a blood culture demonstrating the same baseline pathogen[s])
- Reduced susceptibility to FOS or PIP-TAZ was assessed in the m-MITT population and was defined as a ≥4-fold increase from baseline in minimum inhibitory concentration at Day 5, EOT, TOC, or LFU

METHODS (continued)

Figure 1. ZEUS Study Design



EOT=end of treatment; IV=intravenous; LFU=late follow-up; q8h=every 8 hours; TOC=test of cure.
*Treatment extended up to 14 days for patients with baseline bacteremia.

RESULTS

Patients

- 465 patients were randomized to FOS (*n*=233) or PIP-TAZ (*n*=232); 79.0% (184/233) of patients in the FOS group and 76.7% (178/232) of patients in the PIP-TAZ group were included in the m-MITT population
- In the m-MITT population, patient demographics and baseline disease characteristics were generally balanced between the FOS and PIP-TAZ treatment groups
  - Overall, most patients were women (63.5%) and white (100%), and the mean (SD) age was 50.6 (20.8) years
  - 45.9% (166/362) of m-MITT patients had cUTI, and 54.1% (196/362) had AP
- The identity and frequency of baseline pathogens were similar between treatment groups
  - The most common pathogens were *Escherichia coli* (FOS, 72.3%; PIP-TAZ, 74.7%) and *Klebsiella pneumoniae* (FOS, 14.7%; PIP-TAZ, 14.0%)

Overall Outcomes

- At TOC, the overall success rates based on PFGE molecular typing were 69.0% for FOS and 57.3% for PIP-TAZ, with microbiologic eradication rates of 70.7% and 60.1% for FOS and PIP-TAZ, respectively
- Clinical cure rates were high and similar between treatment groups (FOS, 90.8%; PIP-TAZ, 91.6%)

Outcomes in Patients With Reduced Study Drug Susceptibility

- Reduced study drug susceptibility on subsequent cultures was identified in 7 (3.8%) FOS and 8 (4.5%) PIP-TAZ patients; all had monomicrobial infections **(Table 1)**
  - Of these patients, almost all were aged ≥50 years (93%), men (73%), and white (100%)
  - All patients had a screening diagnosis of complicated disease (defined as presence of underlying functional or anatomical abnormalities of the urogenital tract or presence of diabetes)
  - At TOC, 7/7 FOS patients and 7/8 PIP-TAZ patients with reduced study drug susceptibility had microbiologic persistence; the eighth PIP-TAZ patient had microbiologic eradication at TOC but experienced a recurrent infection with reduced susceptibility at LFU
  - All patients with evidence of reduced study drug susceptibility achieved clinical cures **(Figure 2A)**
  - All clinical cures at TOC in the FOS and PIP-TAZ treatment groups were sustained through LFU **(Figure 2B)**

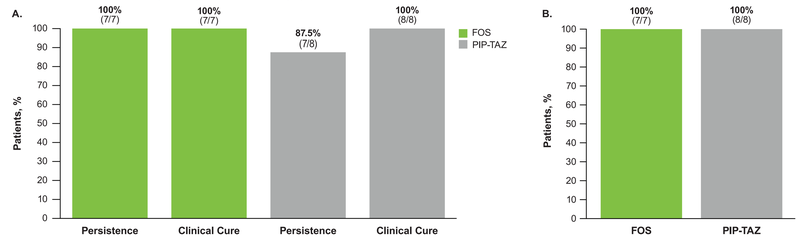
Table 1. Patients With Reduced Study Drug Susceptibility (m-MITT Population)

Treatment Group Patient*	Demographic and Baseline Characteristics						Pathogens That Developed Decreased Susceptibility to Either Study Drug				
	Age, y	Sex	Race	Diagnosis†	Screening Instrumentation		Visit	Uropathogen Identity Based on Molecular Typing (With PFGE Analysis)	Baseline MIC (µg/mL)	Postbaseline MIC (µg/mL)	Fold Change‡
FOS (*n*=7)											
1	59	M	White	cUTI	None		LFU	*Pseudomonas aeruginosa*	64	>512	>8
2	74	M	White	cUTI	Foley catheter		LFU	*Escherichia coli*	0.5	64	128
3	56	M	White	cUTI	None		Day 5	*Klebsiella pneumoniae*	4	32	8
4	69	M	White	cUTI	None		Day 5, EOT, TOC, LFU	*Enterobacter cloacae* species complex	64	≥512	≥8
5	24	M	White	cAP	None		EOT, TOC	*P. aeruginosa*	64	>512	>8
6	56	M	White	cUTI	Suprapubic catheter		TOC	*P. aeruginosa*	64	>512	>8
7	60	M	White	cUTI	None		EOT, TOC	*K. pneumoniae*	16	>512	>32
PIP-TAZ (*n*=8)											
8	50	F	White	cUTI	Stent and Foley catheter		TOC	*E. coli*	1	4	4
9	79	M	White	cUTI	None		TOC	*K. pneumoniae*	4	64	16
10	59	F	White	cUTI	None		LFU	*K. pneumoniae*	1	4	4
11	73	F	White	cUTI	None		TOC	*E. coli*	16	>64	>4
12	79	M	White	cUTI	Suprapubic catheter		LFU	*K. pneumoniae*	2	>64	>32
13	80	M	White	cUTI	Suprapubic catheter		LFU	*K. pneumoniae*	2	64	32
14	79	M	White	cUTI	None		LFU	*K. pneumoniae*	8	32	4
15	57	F	White	cUTI	None		TOC	*E. coli*	2	8	4

AP=acute pyelonephritis; cAP=complicated AP; cUTI=complicated UTI; EOT=end of treatment; F=female; FOS=fosfomycin for injection; LFU=late follow-up; M=male; MIC=minimum inhibitory concentration; m-MITT=microbiologic modified intent to treat; PFGE=pulsed-field gel electrophoresis; PIP-TAZ=piperacillin-tazobactam; TOC=test of cure; UTI=urinary tract infection.
*Patient numbers are arbitrary and do not indicate the same patients between Tables 1 and 2.
†Infection types of AP were classified as uncomplicated or complicated based on the absence or presence, respectively, of underlying functional or anatomical abnormalities of the urogenital tract or presence of diabetes (eg, hypotonic bladder, urinary retention, benign prostatic hypertrophy, nephrolithiasis, various urogenital malignancies, and history of recurrent UTI [history of multiple UTIs, including the current episode], among other comorbidities).
‡Ratio of postbaseline MIC value to baseline MIC value.

RESULTS (continued)

Figure 2. Microbiologic Persistence and Clinical Cure at TOC (A) and Sustained Clinical Cure at LFU (B) in Patients With Reduced Study Drug Susceptibility (m-MITT Population)



FOS=fosfomycin for injection; LFU=late follow-up; m-MITT=microbiologic modified intent to treat; PIP-TAZ=piperacillin-tazobactam; TOC=test of cure.

Outcomes in Patients With Clinical Relapse at LFU

- Although all patients with reduced study drug susceptibility had sustained clinical cures at LFU, a small number of patients (FOS, *n*=8 [4.3%]; PIP-TAZ, *n*=7 [3.9%]) did experience clinical relapse at LFU
- Most patients who experienced clinical relapse at LFU had identifiable explanations or risk factors **(Table 2)**

Table 2. Patients With Clinical Relapse at LFU (m-MITT Population)

Treatment Group Patient	Infection*	Baseline Pathogen and MIC to Study Drug	Microbiologic Response at TOC	Microbiologic Response at LFU	Instrumentation	Relevant Medical History
FOS (*n*=8)						
16	cAP	*Escherichia coli* (MIC 1 µg/mL)	Persistence of *E. coli* (MIC 1 µg/mL)	Continued persistence	None	Diabetes
17	cUTI	*Proteus mirabilis* (MIC 8 µg/mL)	Eradication of *P. mirabilis*; new infection with *Klebsiella pneumoniae* (MIC 8 µg/mL) and *Pseudomonas aeruginosa* (MIC 128 µg/mL)	Indeterminate (no culture)	Nephrostomy tube	Superficial bladder cancer s/p TURB, chronic lymphocytic leukemia, ureterolithiasis
18	uAP	*E. coli* (MIC 0.5 µg/mL)	Persistence of *E. coli* (MIC 1 µg/mL) but eradication based on PFGE typing (unrelated†)	Continued persistence	None	No
19	uAP	*E. coli* (MIC 4 µg/mL)	Persistence of *E. coli* (MIC 2 µg/mL)	Continued persistence	None	No
20	cUTI	*E. coli* (MIC 0.5 µg/mL)	Persistence of *E. coli* (MIC 1 µg/mL)	Continued persistence	None	Diabetes, BPH
21	cUTI	*E. coli* (MIC 1 µg/mL)	Indeterminate (sample lost in transport)	Indeterminate (but regrowth of *E. coli* [MIC 1 µg/mL])	None	Recurrent UTI, post-void residual urine
22	cUTI	*E. coli* (MIC 1 µg/mL)	Persistence of *E. coli* (MIC 512 µg/mL) but likely eradication based on PFGE (unrelated†)	Continued persistence of *E. coli*; new infection with *K. pneumoniae* (MIC 8 µg/mL)	None	Chronic kidney disease, nephrolithiasis, recurrent UTI
23	cUTI	*E. coli* (MIC 1 µg/mL)	Persistence of *E. coli* (MIC 1 µg/mL)	Continued persistence of *E. coli* (MIC 0.5 µg/mL); new infection with *Enterococcus faecalis* (MIC 32 µg/mL)	Stent	Diabetes, recurrent AP, nephrolithiasis, ureterolithiasis
PIP-TAZ (*n*=7)						
24	cAP	*E. coli* (MIC 2 µg/mL)	Persistence of *E. coli* (MIC 2 µg/mL)	Continued persistence	None	Renal colic, recurrent UTI, urolithiasis
25	cUTI	*Klebsiella oxytoca* (MIC >64 µg/mL)	Eradication of *K. oxytoca*; new infection with *E. coli* (MIC 4 µg/mL)	Sustained eradication of *K. oxytoca*; continued growth of *E. coli* (MIC 4 µg/mL)	None	Ureteric stenosis, congenital ureterovesical junction anomaly
26	cUTI	*E. coli* (MIC 2 µg/mL)	Persistence of *E. coli* (MIC 2 µg/mL)	Continued persistence; *E. coli* growth (MIC 2 µg/mL)	None	Diabetes, urinary retention
27	cUTI	*E. coli* (MIC 2 µg/mL)	Persistence of *E. coli* (MIC 2 µg/mL)	Continued persistence; *E. coli* growth (MIC 2 µg/mL)	Intermittent bladder catheterization, Foley catheter	Hydronephrosis, urinary retention, urethral stenosis, nephrectomy
28	cUTI	*K. pneumoniae* (MIC 8 µg/mL)	Eradication of *K. pneumoniae*; new infection with *K. oxytoca* (MIC 4 µg/mL)	Sustained eradication of *K. pneumoniae*; continued growth of *K. oxytoca* (MIC >64 µg/mL)	Foley catheter (inserted on Day –29, removed on Day –2)	Recurrent urethral stricture after surgery, urinary retention
29	cUTI	*E. coli* in blood and urine (MIC 2 µg/mL)	Persistence of *E. coli* in urine (MIC 1 µg/mL)	Continued persistence; *E. coli* in urine (MIC 1 µg/mL)	Stent	Nephrolithiasis, ureterolithiasis
30	AP	*E. coli* (MIC 1 µg/mL)	Persistence of *E. coli* (MIC 1 µg/mL)	Continued persistence	None	Past cystitis

AP=acute pyelonephritis; BPH=benign prostatic hypertrophy; cAP=complicated AP; cUTI=complicated UTI; FOS=fosfomycin for injection; LFU=late follow-up; MIC=minimum inhibitory concentration; m-MITT=microbiologic modified intent to treat; PFGE=pulsed-field gel electrophoresis; PIP-TAZ=piperacillin-tazobactam; s/p=status post; TOC=test of cure; TURB=transurethral resection of the bladder; uAP=uncomplicated AP; UTI=urinary tract infection.
*Infection types of AP were classified as uncomplicated or complicated based on the absence or presence, respectively, of underlying functional or anatomical abnormalities of the urogenital tract or presence of diabetes (eg, hypotonic bladder, urinary retention, benign prostatic hypertrophy, nephrolithiasis, various urogenital malignancies, and history of recurrent UTI [history of multiple UTIs, including the current episode], among other comorbidities).
†Post hoc PFGE typing revealed that the TOC isolate was genetically unrelated to the baseline isolate.

CONCLUSIONS

- In the ZEUS study, few patients had urine isolates with reduced postbaseline susceptibility to either FOS or PIP-TAZ
- No trend was observed in isolate species associated with decreased susceptibility to FOS or PIP-TAZ, including various Enterobacteriaceae species and *Pseudomonas aeruginosa*
- Despite microbiologic persistence at TOC in a small number of patients, all of these patients achieved clinical cures at TOC and sustained cures at LFU, warranting no further antibiotic treatment
- Few cases of clinical relapse were observed at LFU; most patients had identifiable risk factors and a microbiologic response of persistence at TOC

REFERENCES

(1) Bader MS, et al. *Postgrad Med.* 2010;122(6):7-15.
(2) Exner M, et al. *GMS Hyg Infect Control.* 2017;12:Doc05.
(3) Alemayehu D, et al. *Clin Infect Dis.* 2012;55(4):562-567.
(4) Lopez-Montesinos I and Horcajada JP. *Rev Esp Quimioter.* 2019;32 Suppl 1:37-44.
(5) Kahan FM, et al. *Ann N Y Acad Sci.* 1974;235(0):364-386.
(6) Kaye KS, et al. *Clin Infect Dis.* 2019; doi: 10.1093/cid/ciz181:[Epub ahead of print].
(7) Karageorgopoulos DE, et al. *J Antimicrob Chemother.* 2012;67(2):255-268.

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