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In vitro activity of gepotidacin against urine isolates of *Escherichia coli* from outpatient departments in Germany

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Background: *Escherichia coli* is the leading pathogen of community-acquired urinary tract infections. Gepotidacin is a novel, bactericidal, first-in-class triazaacenaphthylene oral antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action that confers activity against most strains of target pathogens, such as *E. coli*, *Staphylococcus saprophyticus* and *Neisseria gonorrhoeae*, including those resistant to other antibiotics.

Objectives: This study assessed the *in vitro* activity of gepotidacin in comparison with ciprofloxacin and other oral standard-of-care antibiotics using a large collection of urine isolates of *E. coli* obtained from outpatients in Germany.

Methods: Four hundred and sixty *E. coli* collected from 23 laboratories during a surveillance study in 2019/2020 were tested. Forty-six isolates (10.0%) produced an ESBL of the CTX-M family, half of which belonged to MDR clonal subgroups of *E. coli* ST131. Antibiotic susceptibilities were tested at a reference laboratory by broth microdilution according to the standard ISO 20776-1.

Results: Fifty-three (11.5%) isolates were ciprofloxacin resistant, 25 (47.2%) of which also produced an ESBL. Overall, $MIC_{50/90}$ values for gepotidacin were 2/4 mg/L (MIC range 0.125–16 mg/L), with no differences in activity between ciprofloxacin-susceptible and ciprofloxacin-resistant isolates, ESBL-producing and non-ESBL isolates, O25b-ST131 isolates, and isolates susceptible or resistant to fosfomycin, mecillinam or nitrofurantoin.

Conclusions: Gepotidacin showed promising *in vitro* activity against urine isolates of *E. coli*, including ciprofloxacin-resistant isolates, ESBL-producing isolates and isolates resistant to oral standard-of-care antibiotics.

Introduction

The management of urinary tract infections (UTIs) in the community is empirical in most cases, and antimicrobial resistance in *Escherichia coli*, the leading pathogen of community-acquired UTIs, to orally administered drugs is a growing serious problem that complicates effective treatment.[1–4] In this context, gepotidacin (formerly GSK2140944), a novel, bactericidal, first-in-class triazaacenaphthylene bacterial type II topoisomerase inhibitor, represents an attractive drug for oral treatment of acute uncomplicated UTI (uUTI).[5] Gepotidacin inhibits bacterial DNA replication through targeting the type II topoisomerases DNA gyrase and topoisomerase IV by a binding mode different from that of the fluoroquinolones.[6,7] The oral formulation of the drug is currently being studied in two Phase III clinical trials for the treatment of uUTI (ClinicalTrials.gov identifiers: NCT04020341 and NCT04187144).

The purpose of this study was to evaluate the *in vitro* activity of gepotidacin in comparison with ciprofloxacin and other oral standard-of-care antibiotics against a collection of *E. coli* urine isolates recovered from outpatient departments across Germany.

Materials and methods

During a laboratory-based surveillance study, 460 *E. coli* urine isolates were collected between October 2019 and March 2020 by the

Table 1. *In vitro* activity of gepotidacin and other oral antibiotics against 460 *E. coli* urine isolates

	MIC (mg/L)			Interpretation (EUCAST)[a]		
Antimicrobial agent	MIC_{50}	MIC_{90}	Range	S (%)	I (%)	R (%)
This study						
Gepotidacin	2	4	0.125–16	Breakpoints not defined		
Ciprofloxacin[b]	0.016	>2	≤0.002 to >2	85.2	3.3	11.5
PEG study						
Amoxicillin	4	>32	≤0.5 to >32	56.7	—	43.3
Amoxicillin/clavulanic acid[c]	4	16	≤0.5 to >32	82.0	—	18.0
Amoxicillin/clavulanic acid[d]	4	16	≤0.5 to >32	94.3	—	5.7
Mecillinam[e]	0.5	4	0.06 to >32	94.8	—	5.2
Cefuroxime[e]	4	>32	≤0.125 to >32	88.7	—	11.3
Cefpodoxime[e]	0.5	>4	≤0.06 to >4	88.9	—	11.1
Cefixime[e]	0.25	4	≤0.03 to >4	89.3	—	10.7
Ciprofloxacin	≤0.06	8	≤0.06 to >8	86.3	2.6	11.1
Trimethoprim/sulfamethoxazole[f]	≤0.25	>16	≤0.25 to >16	72.2	0.9	27.0
Fosfomycin[e]	2	8	≤1–256	92.6	—	7.4
Nitrofurantoin[e]	≤16	32	≤16 to >256	98.9	—	1.1

S=susceptible, standard dosing; I=susceptible, increased exposure; R=resistant.
[a]EUCAST (version 12.0) clinical breakpoints were applied.
[b]Two isolates that tested as resistant to ciprofloxacin (MIC 1 mg/L each) in this study had been classified as S (MIC 0.25 mg/L) and I (MIC 0.5 mg/L), respectively, in the PEG study.
[c]Amoxicillin/clavulanic acid standard breakpoints: S, MIC ≤8 mg/L; R, MIC >8 mg/L.
[d]Amoxicillin/clavulanic acid breakpoints set for isolates from patients with uUTI: S, MIC ≤32 mg/L; R, MIC >32 mg/L.
[e]Breakpoints set for isolates from patients with uUTI.
[f]Trimethoprim/sulfamethoxazole in the ratio 1:19. MICs are expressed as the trimethoprim concentration.

'Antimicrobial Resistance' Study Group of the Paul Ehrlich Society for Infection Therapy (PEG study). Each of the 23 participating laboratories provided 20 isolates. Results of that study have been published elsewhere.[8] In brief, 85.4% isolates were obtained from female patients. Median (IQR) patient age was 63 (45–78) years. Almost half (49.1%) of the isolates were fully susceptible to 10 oral standard-of-care antibiotics representing eight drug classes (penicillins: amoxicillin, mecillinam; penicillins+β-lactamase inhibitors: amoxicillin/clavulanic acid; second-generation cephalosporins: cefuroxime; third-generation cephalosporins: cefixime, cefpodoxime; fluoroquinolones: ciprofloxacin; folate pathway inhibitors: trimethoprim/sulfamethoxazole; phosphonic acids: fosfomycin; nitrofurans: nitrofurantoin), while 21.1% were resistant to 3–6 drug classes. None, however, were resistant to seven or eight drug classes. Ten percent ($n=46$) of the *E. coli* isolates produced an ESBL of the CTX-M family, half of which belonged to MDR clonal subgroups of *E. coli* ST131. Rates of resistance determined for trimethoprim/sulfamethoxazole, fosfomycin, mecillinam and nitrofurantoin, all of which have been recommended for first-line treatment of acute uUTI by current national and international guidelines,[9–11] were 27.0%, 7.4%, 5.2% and 1.1%, respectively.[8]

In this study, MICs were determined according to the broth microdilution (BMD) method described in the International Organization for Standardization (ISO) document 20776-1.[12] BMD test panels for gepotidacin and ciprofloxacin were prepared in-house. Gepotidacin (batch no. 609390010) was supplied by GSK (Stevenage, UK) and ciprofloxacin (batch no. 182CPO) was purchased from Glentham Life Sciences (Corsham, UK). The final concentrations tested were 0.03–32 mg/L (gepotidacin) and 0.002–2 mg/L (ciprofloxacin). The accuracy of susceptibility testing was evaluated using quality control strains *E. coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213.

Isolates were defined as S (susceptible, standard dosing regimen), I (susceptible, increased exposure) or R (resistant) in accordance with the species-related clinical breakpoints approved by EUCAST (version 12.0).[13] Breakpoints for gepotidacin have not been defined yet.

Results

All ciprofloxacin MICs for the quality control strains were within the EUCAST quality control ranges, though the ciprofloxacin MICs against *S. aureus* ATCC 29213 were one $\log_2$ dilution step higher than the calculated target value (0.25 mg/L).[14] Gepotidacin MICs were 1–2 mg/L for *E. coli* ATCC 25922 and 0.25–1 mg/L for *S. aureus* ATCC 29213. These MICs were within the gepotidacin quality control ranges approved by the CLSI.[15]

Fifty-three of the 460 (11.5%) isolates were ciprofloxacin resistant, of which one isolate each had been classified as S (MIC 0.25 mg/L) and I (MIC 0.5 mg/L) in the PEG study, using a commercial BMD test system for susceptibility testing.[8]

Data on the activity of gepotidacin, ciprofloxacin and other oral standard-of-care antibiotics are presented in Table 1.[8] Distributions of the gepotidacin MICs for various susceptible and resistant phenotypes and subsets of isolates are shown in Table 2. Data on the activity of gepotidacin on female patient's isolates can be seen in Tables S1 and S2 (available as Supplementary data at *JAC* Online). Gepotidacin concentrations required to inhibit 50% and 90% of the isolates ($MIC_{50/90}$) were 2/4 mg/L (range, 0.125–16 mg/L). The gepotidacin $MIC_{50/90}$ of

Table 2. MIC distributions of gepotidacin for various susceptible and resistant phenotypes and other subsets of *E. coli* isolates

Subset of isolates[a]	Value type	Gepotidacin (mg/L) ≤ 0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	32	> 32	MIC_{50} (mg/L)	MIC_{90} (mg/L)
Total ($n=460$)	*n*			1	4	3	44	242	141	24	1			2	4
	cum %			0.2	1.1	1.7	11.3	63.9	94.6	99.8	100.0				
Resistant to 3–6 drug classes	*n*				2	1	10	52	26	8				2	4
(MDR, $n=99$)[b]	cum %				2.0	3.0	13.1	65.7	91.9	100.0					
Fully susceptible or resistant to	*n*			1	2	2	34	190	115	16	1			2	4
1–2 drug classes ($n=361$)[b]	cum %			0.3	0.8	1.4	10.8	63.4	95.3	99.7	100.0				
ESBL-producing ($n=46$)	*n*				2		5	25	12	2				2	4
	cum %				4.3		15.2	69.6	95.7	100.0					
Non-ESBL-producing ($n=414$)	*n*			1	2	3	39	217	129	22	1			2	4
	cum %			0.2	0.7	1.4	10.9	63.3	94.4	99.8	100.0				
Ciprofloxacin-resistant ($n=53$)	*n*				2	1	7	24	16	3				2	4
	cum %				3.8	5.7	18.9	64.2	94.3	100.0					
Ciprofloxacin-susceptible ($n=407$)[c]	*n*			1	2	2	37	218	125	21	1			2	4
	cum %			0.2	0.7	1.2	10.3	63.9	94.6	99.8	100.0				
Fosfomycin-resistant ($n=34$)	*n*						6	14	13	1				2	4
	cum %						17.6	58.8	97.1	100.0					
Fosfomycin-susceptible ($n=426$)	*n*			1	4	3	38	228	128	23	1			2	4
	cum %			0.2	1.2	1.9	10.8	64.3	94.4	99.8	100.0				
Mecillinam-resistant ($n=24$)	*n*						1	13	9	1				2	4
	cum %						4.2	58.3	95.8	100.0					
Mecillinam-susceptible ($n=436$)	*n*			1	4	3	43	229	132	23	1			2	4
	cum %			0.2	1.1	1.8	11.7	64.2	94.5	99.8	100.0				
Nitrofurantoin-resistant ($n=5$)	*n*							5						NA	
	cum %							100.0							
Nitrofurantoin-susceptible ($n=455$)	*n*			1	4	3	44	237	141	24	1			2	4
	cum %			0.2	1.1	1.8	11.4	63.5	94.5	99.8	100.0				
AmpC-like ($n=3$)	*n*							1	1	1				NA	
	cum %							33.3	66.7	100.0					
CTX-M group 1 ($n=30$)	*n*				2		2	16	8	2				2	4
	cum %				6.7		13.3	66.7	93.3	100.0					
CTX-M group 9 ($n=15$)	*n*						3	8	4					2	4
	cum %						20.0	73.3	100.0						
CTX-M group 8 ($n=1$)	*n*							1						NA	
	cum %							100.0							
ESBL-producing O25b-ST131[d] ($n=19$)	*n*				1			10	7	1				2	4
	cum %				5.3			57.9	94.7	100.0					
ESBL-producing O16-ST131[d] ($n=4$)	*n*						3	1						NA	
	cum %						75.0	100.0							
Isolates from male patients ($n=67$)	*n*			1		2	6	39	15	4				2	4
	cum %			1.5		4.5	13.4	71.6	94.0	100.0					
Isolates from female patients ($n=393$)	*n*				4	1	38	203	126	20	1			2	4
	cum %				1.0	1.3	10.9	62.6	94.7	99.7	100.0				

NA, data not available; *n*, number of strains; cum %, cumulative % of isolates.

[a]Phenotypes were determined utilizing EUCAST (version 12.0) clinical breakpoints.

[b]Resistance to eight drug classes/subclasses was considered: penicillins (amoxicillin, mecillinam), penicillins + β-lactamase inhibitors (amoxicillin/clavulanic acid; resistant, MIC >8 mg/L), second-generation cephalosporins (cefuroxime), third-generation cephalosporins (cefixime, cefpodoxime), fluoroquinolones (ciprofloxacin), folate pathway inhibitors (trimethoprim/sulfamethoxazole), phosphonic acids (fosfomycin) and nitrofurans (nitrofurantoin).

[c]Susceptible, standard dosing ($n=392$) and susceptible, increased exposure ($n=15$).

[d]PCR-based results (Kresken *et al.* 2022).[8]

the ESBL-producing and non-ESBL-producing as well as ciprofloxacin-resistant and ciprofloxacin-susceptible *E. coli* isolates were also 2 and 4 mg/L, respectively. Gepotidacin $MIC_{50/90}$ values were also 2/4 mg/L against isolates susceptible or resistant to fosfomycin, mecillinam, nitrofurantoin and further subsets of isolates, including isolates producing CTX-M-1 and CTX-M-9 enzymes and O25b-ST131 isolates (four O16-ST131 isolates had gepotidacin MICs ranging from 1 to 2 mg/L). The MIC of ciprofloxacin for the isolate with the highest gepotidacin MIC (i.e. 16 mg/L) was 0.5 mg/L.

Discussion

Antibacterial resistance is increasing due to selective pressure on causative organisms via antibacterial use and transmission of resistance mechanisms. An antibacterial's MIC may increase in the presence of resistance to other antibacterials, leading to unexpected treatment failure.[16] Data from the present study suggest that gepotidacin MICs were unrelated to fluoroquinolone resistance and resistance to other antibacterial drug classes and compare well with the results demonstrated by others.[17,18] Biedenbach *et al.*,[17] investigating a global collection of 1010 *E. coli* isolates collected from 2010 to 2012, reported gepotidacin $MIC_{50/90}$ values of 2/2 mg/L against levofloxacin-susceptible isolates, and $MIC_{50/90}$ values of 2/4 mg/L against isolates that were not susceptible to levofloxacin, nitrofurantoin or fosfomycin. Arends *et al.*[18] tested 1093 *E. coli* isolates collected from 2019 to 2020 from 34 European medical centres located in 17 countries and reported gepotidacin $MIC_{50/90}$ values of 2/2 mg/L for all *E. coli* isolates and 2/4 mg/L for ESBL-producing strains. In this study we found no differences in the gepotidacin $MIC_{50/90}$ values between ciprofloxacin-resistant and ciprofloxacin-susceptible isolates, between MDR and non-MDR isolates, and between ESBL-producing and non-ESBL isolates (2/4 mg/L each). Furthermore, the highest gepotidacin MIC determined in the present study was 16 mg/L. Arends *et al.*[18] reported 32 mg/L as the highest MIC and Biedenbach *et al.*[17] detected five geographically unrelated *E. coli* with gepotidacin MICs of ≥16 mg/L. The reason for these higher MIC values is unclear so far. Studies by Schuster *et al.*[19] indicate possible overexpression of the AcrAB-TolC efflux pump system. However, while efflux has been demonstrated to have an effect on the *in vitro* activity of gepotidacin, further investigation would be needed to elucidate the cause of the elevated gepotidacin MIC for the one *E. coli* isolate with a gepotidacin MIC of 16 mg/L.[20,21] Furthermore, in the absence of breakpoints for gepotidacin, the clinical relevance of the higher MICs and gepotidacin susceptibility cannot be determined.

Currently, two Phase III clinical trials are being performed in female patients ≥12 years of age to compare the efficacy and safety of gepotidacin with nitrofurantoin in the treatment of uUTI. Patients are administered oral doses of 1500 mg gepotidacin every 12 h for 5 days (ClinicalTrials.gov identifiers: NCT04020341 and NCT04187144). In a prior Phase IIa study including 22 eligible female patients with uUTI, pre-dose concentrations of gepotidacin in urine achieved on Day 2 to Day 5 ranged from 26.8 to 4540 mg/L, which were above the highest gepotidacin MIC (16 mg/L) determined for *E. coli* isolates recovered from urine in Germany in the present study.[5]

In conclusion, gepotidacin may represent a favourable new oral option for the treatment of uUTI, particularly when resistance to other oral standard-of-care antibiotics is suspected or confirmed, including for MDR infections.

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Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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