Ian A. Critchley
ID Week
October 2020
Presentation Number:
Submission ID: 904232
Poster 1695

Tebipenem: An oral carbapenem with activity against multi-drug resistant urinary tract infection isolates of *Escherichia coli* collected from US medical centers during 2019

I.A. Critchley[1], N. Cotroneo[1], M.J. Pucci[1], A. Jain[1], R.E. Mendes[2]

[1]Spero Therapeutics, Cambridge, MA, [2]JMI Laboratories, North Liberty, IA

Spero Therapeutics
675 Massachusetts Ave
14th Floor
Cambridge, MA 02139
Phone: (303) 564-5139
E-mail: icritchley@sperotherapeutics.com

ABSTRACT

Background: *Escherichia coli* (EC) is a predominant urinary tract infection (UTI) pathogen where increasing prevalence of extended spectrum-β-lactamase (ESBL) continues to compromise the use of currently available oral antibiotics. ESBL-producing EC exhibit coresistance to the fluoroquinolones (FQs) and trimethoprim-sulfamethoxazole (TMP-SMX) making treatment of UTIs outside the hospital difficult and intravenous (IV) agents are often needed. Tebipenem (TBP) is an oral carbapenem with similar activity to IV carbapenems in clinical development for treating complicated UTIs (cUTI). This study assessed the activity of TBP against EC collected from UTIs in the US including isolates R to oral agents.
Methods: 1133 EC from UTIs in the 2019 STEWARD Surveillance Program were tested for susceptibility to TBP and comparators. Isolates were collected from medical centers geographically distributed across the US Census regions, centrally tested, and susceptibility (S) interpreted according to CLSI criteria.

Results: Overall prevalence of ESBL EC from UTI was 15.4% and R to oral cefuroxime, levofloxacin and TMP-SMX were: 15.6%, 23.9% and 33.5%, respectively. In contrast, low R was observed for the IV carbapenems. All EC were inhibited by TBP at ≤0.5 µg/mL and the MIC_{90} was 0.015 µg/mL compared with MIC_{90}s of 0.03 µg/mL for meropenem (MER) and ertapenem (ETP). Using a tentative PK/PD cut off of 0.12 µg/mL 99.7% of EC were inhibited by TBP. The MIC_{90}s for LEV and TMP-SMX were 32 and >16 µg/mL, respectively, against ESBL EC with R rates at ≥66.3%. MIC_{90}s of 0.03, 0.03 and 0.12 µg/mL, respectively, were noted for TBP, MER (100% S) and ETP (99.6% S). TBP was active against LEV-R, TMP-SMX-R and MDR (≥3 classes) EC with MIC_{90}s of 0.03 µg/mL.

Conclusions: R to oral agents remains high, raising concerns on empiric use. Carbapenems remain active against EC due to their stability to ESBLs and are not compromised by co-resistance. TBP is an oral carbapenem with similar activity to IV carbapenems based on comparison of MIC_{90} values. Although no breakpoints are available, ≥99.7% of EC were inhibited by TBP at ≤0.12 µg/mL highlighting potential as a new oral option for cUTIs in an era of ESBL mediated co-resistance to the FQs and TMP-SMX

INTRODUCTION

Urinary tract infections caused by *E. coli,* the most prevalent UTI pathogen, have been historically managed with oral antibiotics including the cephalosporins, TMP-SMX and the fluoroquinolones. The utility of many of these agents is being eroded by widespread use and development of resistance. The increasing prevalence of extended spectrum β-lactamases (ESBLs) among gram-negative uropathogens compromises the use of oral β-lactams and poses additional risk, including longer durations of hospital stay. Of concern are the high levels of antimicrobial co-resistance among ESBL-producing organisms that render many of the currently available oral agents used to treat UTIs less effective. Recent surveillance studies have shown that the only agents that remain highly active against ESBL-producing *E. coli* are the intravenous (IV) carbapenems because of their inherent stability to β-lactamases other than carbapenemase enzymes. Oral agents with the spectrum and potency of the carbapenems would address the unmet need for newer tx options for cUTIs caused by resistant pathogens. Tebipenem is an oral carbapenem that has recently demonstrated non-inferiority to IV ertapenem for the treatment of cUTI. The goal of the study was to evaluate the activity of tebipenem and comparators agents against contemporary UTI pathogens collected in the US during 2019 that included ESBL phenotypes, levofloxacin-resistant and TMP-SMX-resistant organisms.

METHODS

A total of 1,131 isolates of *E. coli* were collected as part of the STEWARD Surveillance Program (JMI Laboratories, North Liberty, IA) from 47 participating medical centers geographically distributed across the nine Census regions of the US. Isolates were collected from patients with UTI; urine/urinary tract (n = 984), ureteral catheter (n = 111), and urethral Foley catheter (n = 37). Isolates were from both nosocomial and community-acquired infections and included both complicated and uncomplicated UTIs. Only isolates determined to be significant by local criteria as the reported probable cause of infection were included in the study. Species identification was confirmed using standard biochemical tests and using a MALDI Biotyper according to manufacturer's instructions. All isolates were centrally tested using the broth microdilution method in accordance with CLSI guidelines. Antibiotics evaluated in the study included various oral antibiotics routinely used to treat UTIs including the cephalosporins, fluoroquinolones and trimethoprim-sulfamethoxazole (TMP-SMX), as well as the intravenous carbapenems. ESBL phenotypes were determined in accordance with CLSI MIC screening criteria. CLSI interpretive criteria for the Enterobacterales were used to determine susceptibility rates for all agents including levofloxacin and TMP-SMX.

RESULTS

Figure 1: National and regional prevalence of ESBL, levofloxacin and TMP-SMX-resistant phenotypes among 1,133 *E. coli* from UTI in the USA in 2019 STEWARD Surveillance

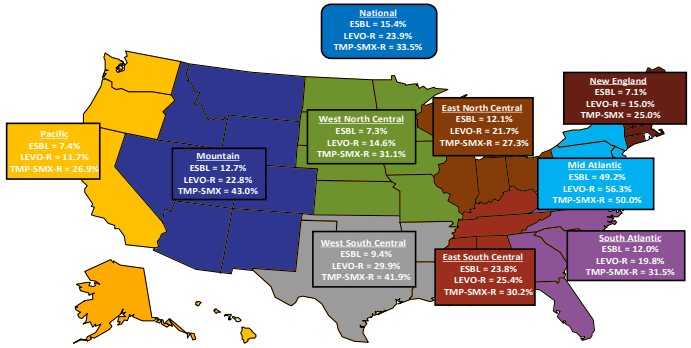

Table 1: Activity of tebipenem and comparator agents against 1,133 UTI isolates of *E. coli* collected in the US during 2019 surveillance

Antimicrobial Agent	Range	MIC_{50}	MIC_{90}	CLSI		
				%S	%I	%R
Tebipenem	≤0.004 - 0.5	0.015	0.015			
Ertapenem	≤0.008 - 2	≤0.008	0.03	99.6	0.3	0.1
Imipenem	≤0.12 - 2	≤0.12	≤0.12	99.9	0.1	0
Meropenem	≤0.015 - 1	≤0.015	0.03	100	0	0
Levofloxacin	≤0.015 - >32	0.03	16	75.3	0.8	23.9
TMP-SMX	≤0.12 - >16	≤0.12	>16	66.5		33.5
Cefuroxime	≤0.5 - >64	4	>64	58.9	25.5	15.6
				80.8	3.5	15.6
Amoxicillin-clavulanic acid	0.5 - >32	4	16	80.5	14.1	5.4
Mecillinam	≤0.06 - >8	0.5	>8	NA	NA	NA
Nitrofurantoin	≤4 - >64	16	32	96.3	1.8	1.9
Amikacin	≤0.25 - >32	2	4	99.6	0.2	0.2
Aztreonam	≤0.03 - >16	0.12	8	87.1	3.6	9.3
Ceftazidime	0.03 - >32	0.25	8	89.1	2.8	8.1
Ceftriaxone	≤0.06 - >8	≤0.06	>8	85.3	0.4	14.3

Figure 3: Resistance to oral and IV agents among 175 ESBL phenotypes of *E. coli* from UTIs

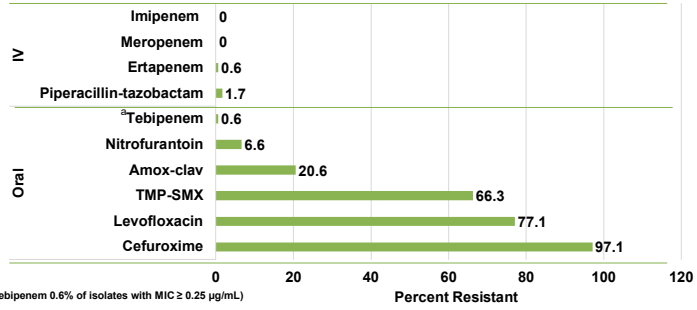

Figure 2: MIC distributions for tebipenem and ESBL/non-ESBL phenotypes of *E. coli* from UTIs

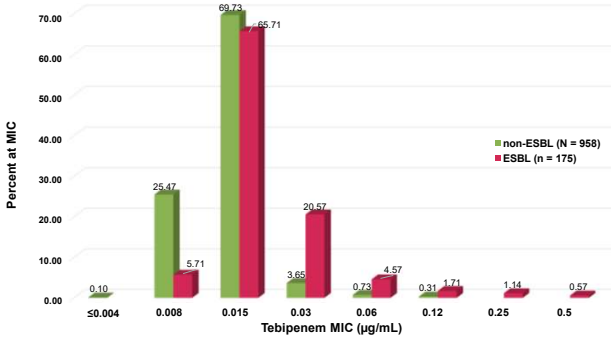

Table 2: Activity of tebipenem against multi-drug resistant *E. coli* from UTIs

E. coli Phenotype	N	Tebipenem MIC (µg/mL)		
		Range	50%	90%
All	1133	≤0.004 – 0.5	0.015	0.015
non ESBL	958	≤0.004 – 0.12	0.015	0.015
ESBL	175	0.008 – 0.5	0.015	0.03
Levofloxacin-R	270	0.008 – 0.25	0.015	0.03
ESBL and Levofloxacin-R	135	0.008 – 0.25	0.015	0.03
TMP-SMX-R	377	0.008 – 0.25	0.015	0.03
Levofloxacin + TMP-SMX-R	166	0.008 – 0.25	0.015	0.03

CONCLUSIONS

Among UTI isolates of *E. coli* the national prevalence rate of ESBL phenotypes was 15.4% and ranged from 7.3% in West North Central to 49.2% in Mid-Atlantic (Figure 1). National resistance rates for levofloxacin and TMP-SMX were 23.9% and 33.5%, respectively.

Carbapenems remained active with ≥99.6% of the UTI *E. coli* isolates being reported as susceptible to ertapenem, imipenem and meropenem (Table 1). The oral carbapenem, tebipenem exhibited similar activity to iv carbapenems with an MIC_{90} value of 0.015 µg/mL and all isolates inhibited at ≤0.5 µg/mL.

Tebipenem exhibited similar activity against both ESBL and non-ESBL phenotypes of *E. coli* from UTIs (Figure 2). The modal MIC was 0.015 µg/mL against both phenotypes

Among ESBL phenotypes of *E. coli* high co-resistance was observed for currently available oral agents (amox-clav, TMP-SMX, levofloxacin and cefuroxime) (Figure 3). No breakpoints are currently available for tebipenem, but preliminary PK/PD data support a breakpoint of 0.12 µg/mL but only 0.6% of *E. coli* exhibited MICs ≥0.25 µg/mL.

Tebipenem maintained activity against ESBL+, levofloxacin-R and TMP-SMX-R phenotypes of *E. coli* with MIC_{90},s of 0.03 µg/mL regardless of resistance phenotype (Table 2). Tebipenem represents a new oral option for cUTIs in an era of ESBL-mediated co-resistance to existing oral agents.

ACKNOWLEDGEMENT

This research was funded in part with Federal funds from DHS, ASPR, and BARDA under Contract No. HHSO100201800015C