Efficacy and Safety of Ceftolozane/Tazobactam Versus Meropenem in the Treatment of Complicated Intra-abdominal Infections (cIAI) in Hospitalized Adults: Results From the Phase 3 ASPECT-cIAI Trial

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INTRODUCTION

- Complicated intra-abdominal infections (cIAIs) are an important cause of morbidity and are associated with mortality in approximately 10% of patients.[1]
- An important feature of cIAI is the high level of antimicrobial resistance among the Gram-negative pathogens that are commonly isolated (*Escherichia coli, Klebsiella pneumoniae,* and *Pseudomonas aeruginosa*).[2]
- The rate of extended-spectrum β-lactamase (ESBL)–producing isolates in *E. coli* and *K. pneumoniae* has increased during recent years,[2] warranting the development of new agents.
- Ceftolozane/tazobactam (TOL/TAZ) is a novel antibacterial agent with activity against common Gram-negative pathogens, including ESBL-producing Enterobacteriaceae and drug-resistant *P. aeruginosa*.[3,4]
- The efficacy and safety of TOL/TAZ plus metronidazole (MTZ) versus meropenem (MEM) for the treatment of hospitalized adults with cIAI were evaluated based on pooled data from 2 identical Phase 3, multicentre, randomized, double-blind trials (NCT01445665 and NCT01445678).

OBJECTIVES

- Primary: To demonstrate the noninferiority (NI) of TOL/TAZ+MTZ versus MEM based on the difference in clinical cure rates at the test-of-cure (TOC) visit (26-30 days after initiation of treatment).
- To evaluate the microbiological response at the TOC visit and to assess safety and tolerability.

METHODS

Study Design

- Double-blind, active-controlled NI trial enrolling hospitalized adult patients with cIAI who required surgical intervention. Patients were randomized to receive TOL/TAZ 1.5 g (containing 1000 mg ceftolozane and 500 mg tazobactam) every 8 hours (q8h) + MTZ (500 mg q8h) or MEM (1 g q8h) + placebo for 4 to 14 days. Intra-abdominal specimens were collected for culture at baseline.
- Clinical response was classified as:
  - Clinical cure: Complete resolution/significant improvement of the index infection, with no additional antibiotics or surgical procedure required.
  - Clinical failure: Death due to cIAI, persistent/recurring infection requiring additional intervention, requirement for additional antibiotics for ongoing cIAI, postsurgical wound infection.
  - Indeterminate: Study data were not available for evaluation of efficacy for any reason, including death during the study period, or extenuating circumstances that precluded classification as cure or failure.

METHODS (cont'd)

Key Inclusion Criteria

- Men and women aged ≥18 years.
- Diagnosis of intra-abdominal abscess or peritonitis due to perforation of a hollow viscus, or infection following previous intra-abdominal operation.

Statistical Analysis

- For the European Medicines Agency's (EMA) defined endpoints, NI in clinical cure rates was tested using an NI margin of 12.5% at a 1-sided alpha of 0.005 in the clinically evaluable (CE; primary) and intent-to-treat (ITT; secondary) populations.
- For the US Food and Drug Administration's (FDA) defined endpoints, NI in clinical cure rates was tested using an NI margin of 10% at a 1-sided alpha of 0.025 in the microbiological ITT (MITT; primary) and microbiologically evaluable (ME; secondary) populations.

Source Control Review

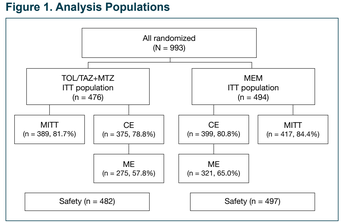
- To evaluate the antibiotic effect, cases considered clinical failures and all patients considered cures but undergoing a second procedure were reviewed by an independent Surgical Review Panel (SRP, comprising 3 surgeons and 2 interventional radiologists) for exclusion of patients who had received a poorly chosen or poorly executed intervention strategy. Reviewers were unaware of patient treatment allocations.

RESULTS

Patient Disposition and Baseline Characteristics

- A total of 993 patients were enrolled from Europe, North America, South America, and other geographical regions (**Figure 1**).

Figure 1. Analysis Populations



ITT: all randomized patients, regardless of whether they received study drug. 23 patients were excluded from the ITT population due to concerns regarding data integrity.
MITT: all randomized patients who had ≥1 baseline pathogen, regardless of the susceptibility to study drug.
CE: the subset of ITT patients who received an adequate amount of study drug, met the protocol definition of cIAI, adhered to study procedures, and had a TOC visit within the specified window.
ME: the subset of CE patients who had ≥1 baseline pathogen that was susceptible to study drug received.
Safety population: all patients who received any amount of study drug.

RESULTS (cont'd)

- Baseline demographics and infection characteristics were similar between the treatment groups (**Table 1**).

Table 1. Demographic and Infection Characteristics at Baseline (ITT Population)

	TOL/TAZ+MTZ (n = 476)	MEM (n = 494)
Sex, male, n (%)	266 (55.9)	300 (60.7)
Race, white, n (%)	448 (94.1)	459 (92.9)
Age, y, mean (SD)	50.7 (17.9)	50.7 (16.8)
Age ≥ 65 y, n (%)	116 (24.4)	105 (21.3)
Body mass index, kg/m², mean (SD)	26.8 (5.5)	27.0 (5.1)
Baseline APACHE II category, n (%)[a]		
<10	387 (81.3)	409 (82.8)
≥10	88 (18.5)	82 (16.6)
Creatinine clearance, mL/min, n (%)		
Normal (≥80)	333 (70.0)	350 (70.9)
Mild renal impairment (>50-<80)	116 (24.4)	125 (25.3)
Moderate renal impairment (≥30-≤50)	27 (5.7)	16 (3.2)
Severe renal impairment (<30)	(0.0)	1 (0.2)
Origin of current infection, n (%)		
Stomach/duodenum	61 (12.8)	55 (11.1)
Biliary - cholecystitis	91 (19.1)	96 (19.4)
Biliary - cholangitis	2 (0.4)	1 (0.2)
Small bowel	28 (5.9)	21 (4.3)
Appendix	209 (43.9)	219 (44.3)
Colon	59 (12.4)	70 (14.2)
Parenchymal (liver)	19 (4.0)	22 (4.5)
Parenchymal (spleen)	4 (0.8)	3 (0.6)
Peritonitis present, n (%)	398 (83.6)	396 (80.2)
Localized complicated appendicitis, n (%)	138 (29.0)	150 (30.4)
Procedure type, n (%)[a]		
Laparotomy	327 (68.7)	317 (64.2)
Laparoscopy	108 (22.7)	127 (25.7)
Percutaneous aspiration	33 (6.9)	43 (8.7)
Other	6 (1.3)	5 (1.0)

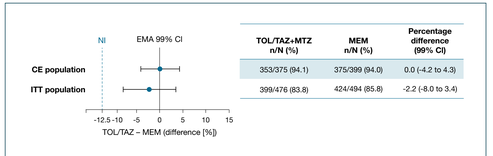
APACHE II, Acute Physiology and Chronic Health Evaluation II.
[a]Baseline data were not available for all patients.

- The most common diagnosis was appendiceal perforation or periappendiceal abscess, occurring in 420/970 (43.3%) patients.
- Enterobacteriaceae were the most common pathogens, with a TOL/TAZ minimum inhibitory concentration required to inhibit the growth of 90% of organisms (MIC_{90}) of 1 mg/L; the overall ESBL rate was 7.2%.
- The SRP reviewed 73 patients, 64 as failures and 9 as cures with a second procedure. Of the 64 failures, 24 were considered to have had an inadequate procedure and were removed from the CE and ME populations. The SRP considered 2/9 cures with second procedures as failures.

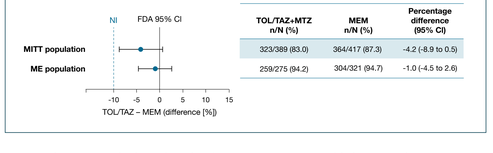
Efficacy

- The clinical cure rates at the TOC visit with TOL/TAZ+MTZ were NI to those with MEM for the CE and ITT populations (ie, the lower bound of the 2-sided 99% confidence interval [CI] for the difference in cure rates was greater than -12.5%) (**Figure 2**).
- The clinical cure rates at the TOC visit with TOL/TAZ+MTZ were NI to those with MEM for the MITT and ME populations (ie, the lower bound of the 2-sided 95% CI for the difference in cure rates was greater than -10%) (**Figure 2**).

Figure 2. Primary and Key Secondary Analysis Endpoints at the TOC Visit (CE, ITT, MITT, and ME Populations)



	TOL/TAZ+MTZ n/N (%)	MEM n/N (%)	Percentage difference (99% CI)
CE population	353/375 (94.1)	375/399 (94.0)	0.0 (-4.2 to 4.3)
ITT population	399/476 (83.8)	424/494 (85.8)	-2.2 (-8.0 to 3.4)



	TOL/TAZ+MTZ n/N (%)	MEM n/N (%)	Percentage difference (95% CI)
MITT population	323/389 (83.0)	364/417 (87.3)	-4.2 (-8.9 to 0.5)
ME population	259/275 (94.2)	304/321 (94.7)	-1.0 (-4.5 to 2.6)

- Per-pathogen microbiological eradication rates were comparable between the 2 treatment arms (**Table 2**).
- The microbiological eradication rates for the 2 most common Enterobacteriaceae were 193/201 (96.0%) versus 214/225 (95.1%) for *E. coli* and 28/28 (100%) versus 22/25 (88.0%) for *K. pneumoniae* for the TOL/TAZ+MTZ and MEM groups, respectively.
- Against *P. aeruginosa*, the microbiological eradication rates for TOL/TAZ+MTZ and MEM were 25/25 (100%) and 28/28 (100%), respectively.

Table 2. Per-pathogen Microbiological Eradication Rate (ME Population)

Key Pathogens, n (%)[a]	TOL/TAZ+MTZ (n = 275)	MEM (n = 321)
Gram-negative aerobes	234/243 (96.3)	269/282 (95.4)
E. coli	193/201 (96.0)	214/225 (95.1)
K. pneumoniae	28/28 (100)	22/25 (88.0)
P. aeruginosa	25/25 (100)	28/28 (100)
Enterobacter cloacae	18/21 (85.7)	22/22 (100)
Proteus mirabilis	10/11 (90.9)	9/10 (90)
Klebsiella oxytoca	12/12 (100)	21/22 (95.5)
Gram-negative anaerobes[b]	107/109 (98.2)	134/137 (97.8)
Bacteroides fragilis	39/41 (95.1)	56/57 (98.2)
Bacteroides ovatus	37/37 (100)	42/56 (98.2)
Gram-positive aerobes[b]	131/141 (92.9)	158/167 (94.6)
Streptococcus anginosus	28/30 (93.3)	23/23 (100)
Enterococcus faecalis	28/32 (87.5)	33/35 (94.3)
Gram-positive anaerobes	34/34 (100)	46/49 (93.9)
Clostridium perfringens	15/15 (100)	18/19 (94.7)

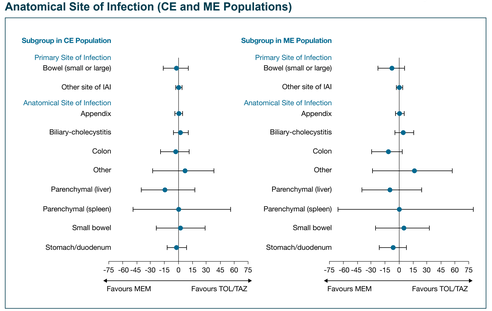
[a]Data are presented for pathogens isolated in ≥10 patients in the TOL/TAZ+MTZ treatment group.
[b]Data are presented for the 2 most commonly isolated pathogens.

- Clinical cure rates by anatomical site of infection with TOL/TAZ+MTZ and MEM were similar (**Figure 3**).
- Clinical cure for ESBL-producing Enterobacteriaceae was achieved in 22/22 (100%) and 23/26 (88.5%) patients in the TOL/TAZ+MTZ and MEM treatment groups, respectively (**Table 3**).
  - For patients with *E. coli*-producing CTX-M-14 or CTX-M-15 ESBLs, clinical cure rates were 9/9 (100%) and 7/9 (77.8%) for the TOL/TAZ+MTZ and MEM treatment groups, respectively.

Safety

- The safety profiles of the 2 treatments were comparable (**Table 4**).
- The most commonly reported adverse events (AEs) in the TOL/TAZ+MTZ and MEM groups were nausea (7.9% vs 5.8%), diarrhoea (6.2% vs 5.0%), and pyrexia (5.2% vs 4.0%). The rate of serious AEs was 8.1% and 7.2% for the TOL/TAZ+MTZ and MEM treatment arms, respectively. Drug-related serious AEs were rare, occurring in only 1 patient in each treatment group (both *Clostridium difficile* infections that resolved).
- There were 11 deaths in the TOL/TAZ+MTZ group and 8 deaths in the MEM group; none were considered drug-related.

Figure 3. Clinical Response at the TOC Visit by Primary Site of Infection and by Anatomical Site of Infection (CE and ME Populations)



95% CIs for the difference of (TOL/TAZ + MTZ) – MEM are calculated as Wilson Score CIs. A patient can have more than 1 anatomical site of infection. A data-as-observed approach was used for the calculation of Wilson Score CIs.

Table 3. Per-pathogen Clinical Response by ESBL Status of Enterobacteriaceae at the TOC Visit (ME Population)

Pathogen, n (%)	TOL/TAZ+MTZ (n = 275)	MEM (n = 321)
Enterobacteriaceae		
All ESBL	22/22 (100)	23/26 (88.5)
CTX-M-14, CTX-M-15	12/12 (100)	8/11 (72.7)
E. coli		
All ESBL	14/14 (100)	18/20 (90.0)
CTX-M-14, CTX-M-15	9/9 (100)	7/9 (77.8)
K. pneumoniae		
All ESBL	6/6 (100)	3/4 (75.0)
CTX-M-14, CTX-M-15	4/4 (100)	0/1 (0)

Table 4. AEs in ≥2% of Patients in Either Arm (Safety Population)

AE, n (%)	TOL/TAZ+MTZ (n = 482)	MEM (n = 497)
Any AE	212 (44.0)	212 (42.7)
Nausea	38 (7.9)	29 (5.8)
Diarrhoea	30 (6.2)	25 (5.0)
Vomiting	16 (3.3)	20 (4.0)
Pyrexia	25 (5.2)	20 (4.0)
Hypokalaemia	14 (2.9)	8 (1.6)
Insomnia	17 (3.5)	11 (2.2)
Headache	12 (2.5)	9 (1.8)
Anaemia postoperative	10 (2.1)	8 (1.6)
Hypertension	9 (1.9)	10 (2.0)

CONCLUSIONS

- Ceftolozane/tazobactam + metronidazole in cIAI
  - was noninferior to meropenem in clinical cure rates for both primary and key secondary analyses;
  - achieved high rates of microbiological eradication against Enterobacteriaceae and *P. aeruginosa*;
  - demonstrated high clinical cure rates against ESBL-producing Enterobacteriaceae, comparable to meropenem;
  - was generally well tolerated.
- These data suggest that ceftolozane/tazobactam + metronidazole is a useful treatment option for patients with cIAI, including infections caused by drug-resistant pathogens.

REFERENCES

1. Sartelli M, et al. *World J Emerg Surg.* 2013;8:1.
2. Babinchak T, et al. *Diagn Microbiol Infect Dis.* 2013;76:379-381.
3. Farrell D J, et al. *Antimicrob Agents Chemother.* 2013;57:6305-6310.
4. Walkty A, et al, *Antimicrob Agents Chemother.* 2013;57:5707-5709.

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