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Original Article

The efficacy and safety of tazobactam/ceftolozane in combination with metronidazole in Japanese patients with complicated intra-abdominal infections[☆]

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A B S T R A C T

Tazobactam/ceftolozane, a novel antimicrobial therapy, is active against *Pseudomonas aeruginosa* and most extended-spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*. We report the results of the efficacy and safety of tazobactam/ceftolozane in Japanese patients with complicated intra-abdominal infections (cIAI).

A multicenter, open-label, noncomparative study (MK-7625A Protocol 013, ClinicalTrials.gov Identifier: NCT02739997) to investigate the efficacy and safety of tazobactam/ceftolozane used in combination with metronidazole in Japanese patients with cIAI was conducted. One hundred Japanese patients with cIAI received tazobactam/ceftolozane 1.5 g (tazobactam 0.5 g/ceftolozane 1 g) plus metronidazole 500 mg intravenously every 8 h for 60 min for 4–14 days. The clinical response rate at the Test-of-Cure visit (TOC; Day 28 ± 2 days) was 92.0% (81/88 subjects). By disease type, the clinical response rates were 92.3% (24/26) for cholecystitis, 100% (6/6) for liver abscess, 93.5% (58/62) for intra-abdominal abscess and 90.2% (55/61) for peritonitis. The per-subject microbiological response rate at the TOC was 90.2% (55/61). Per-pathogen microbiological response rates in the most common baseline pathogens were *Escherichia coli* 90.2% (37/41), *Kebsiella pneumoniae* 91.7% (11/12), *Streptococcus anginosus* 100% (11/11), *Streptococcus constellatus* 90.0% (9/10) and *Bacteroides fragilis* 95.2% (20/21). The most common drug-related AEs were aspartate aminotransferase increased (11.0%) and alanine aminotransferase increased (9.0%). No serious drug-related AE was reported during the study.

The favorable effect of tazobactam/ceftolozane in the treatment of cIAI suggests that the agent will be useful in clinical practice in Japan.

1. Introduction

Complicated intra-abdominal infections (cIAI) are common infections [1], and are sometimes associated with poor outcomes, significant morbidity and mortality [2]. cIAI is estimated to be responsible for 20% of all severe sepsis episodes in the intensive care unit [3]. In a large retrospective cohort study, inappropriate choice of initial antibiotic therapy in patients with secondary IAI resulted in higher rates of clinical failure resulting in longer hospital stays and higher costs of hospitalization [4]. Pathogens most commonly encountered in cIAI are *E. coli*, other common *Enterobacteriaceae*, *P. aeruginosa*, and *B. fragilis* [5]. Cephalosporins in

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combination with antianaerobic agent, extended-spectrum penicillin/beta (β)-lactamase inhibitors (BLIs), and carbapenems are commonly used for the treatment of cIAI [6].

Increasing resistance to these commonly prescribed antimicrobial agents is a serious global problem. The main resistance threat in IAI is posed by extended spectrum β-lactamase (ESBL)-producing *Enterobacteriaceae*, which are becoming increasingly common in community acquired infections. The frequency of ESBL-producing *E. coli* isolates and ESBL-producing *K. pneumoniae* isolates collected from patients with IAI increased from 2002 to 2011 as a world trend [7].

Tazobactam/ceftolozane (TAZ/CTLZ) is a combination of the novel antibiotic, ceftolozane and the established BLI, tazobactam. Ceftolozane is a member of the cephalosporin class and active against gram-negative aerobes including multidrug-resistant *P. aeruginosa*. Combining ceftolozane with tazobactam, broadens its in vitro spectrum to antibiotic resistant *Enterobacteriaceae* and is, thereby, likely to improve its clinical utility as a therapy for serious bacterial infections caused by resistant gram-negative bacteria.

Global, prospective, randomized, double-blind large Phase 3 trials of TAZ/CTLZ in non-Japanese subjects with cIAI (ClinicalTrials.gov Identifier: NCT01445678) and complicated urinary tract infection (cUTI) (ClinicalTrials.gov Identifier: NCT01345929) were previously completed. The results indicated that TAZ/CTLZ plus metronidazole was non-inferior to meropenem for the primary efficacy endpoints in cIAI [8] and TAZ/CTLZ was non-inferior and superior to levofloxacin for the primary efficacy endpoints in cUTI [9]. TAZ/CTLZ is approved in the United States (December 2014), the European Union (September 2015) and other regions for cIAI and cUTI.

In Japan, a local phase 3 study in Japanese subjects with cIAI was conducted to further confirm the safety and efficacy of TAZ/CTLZ in Japanese population. We report the results of the efficacy and safety of TAZ/CTLZ in Japanese patients with cIAI.

2. Patients and methods

2.1. Study design and target population

This study was a multicenter, open-label, noncomparative study (MK-7625A Protocol 013, ClinicalTrials.gov Identifier: NCT02739997) to investigate the efficacy and safety of TAZ/CTLZ used in combination with metronidazole in Japanese patients with cIAI, conducted at a total of 37 sites in Japan from April 2016 through July 2017.

The inclusion criteria for cIAI were 1) one of the following diagnoses with evidence of intra-peritoneal infection: cholecystitis (including gangrenous cholecystitis) with rupture, perforation, or progression of the infection beyond the gallbladder wall; diverticular disease with perforation or abscess; appendiceal perforation or periappendiceal abscess; acute gastric or duodenal perforation; traumatic perforation of the intestine; peritonitis due to perforated viscus or following a prior operative procedure; or intra-abdominal abscess (including liver and spleen), 2) evidence of systemic infection, 3) had or had plans to have surgical intervention within 24 h of the first dose of study drug, 4) radiographic evidence of perforation or abscess if enrolled preoperatively, 5) ability to have intra-abdominal specimen taken at baseline for the microbiological assessment. Patients were 18 years of age or older at the time of consent.

The patient who met any of the following criteria was to be excluded: 1) simple appendicitis; abdominal wall abscess; small bowel obstruction or ischemic bowel disease without perforation; spontaneous bacterial peritonitis associated with cirrhosis and chronic ascites; acute suppurative cholangitis; infected necrotizing pancreatitis; pancreatic abscess; infectious mononucleosis; cystic fibrosis; or pelvic infections, 2) acute gastric or duodenal perforation operated on ≤24 h or traumatic perforation of the intestine operated on ≤12 h after the perforation occurred, 3) used systemic antibacterial therapy for intra-abdominal infection for more than 24 h during the previous 72 h prior to the first dose of study drug, unless there was a documented treatment failure with such therapy, 4) severe impairment of renal function (estimated creatinine clearance [CrCl] <30 mL/min), 5) used any postoperative non-study antibacterial therapy if enrolled preoperatively, or used more than 1 dose of non-study antibacterial therapy following surgery if enrolled postoperatively, 6) hepatic disease (total bilirubin >2 × ULN, alkaline phosphatase, alanine aminotransferase or aspartate aminotransferase >4 × ULN), 7) receiving or received disulfiram within 14 days before receiving study drug or who was currently receiving probenecid.

Prior to the initiation of the study, informed consent was obtained from each potential patient or legal guardians to participate in this study of her/his own free will. This study was approved by the Institutional Review Board (IRB), and conducted in compliance with Good Clinical Practice (GCP) and Declaration of Helsinki.

2.2. Study methods

Patients received TAZ/CTLZ 1.5 g (tazobactam 0.5 g/ceftolozane 1 g) intravenously every 8 h for 60 min for 4–14 days. Duration of therapy was based on clinical resolution or significant improvement of the index infection at the discretion of the investigator under unblinded conditions. Patients with CrCl of 30–50 mL/min received TAZ/CTLZ 750 mg (tazobactam 250 mg/ceftolozane 500 mg) for the same treatment period. Patients also received metronidazole 500 mg intravenously every 8 h for 60 min for 4–14 days to cover anaerobic pathogens other than *B. fragilis* as TAZ/CTLZ may not show activity against those anaerobes.

At baseline, intra-abdominal specimens were collected from aspirates (collected with a needle or a syringe), tissue or biopsy samples for culture of aerobes and anaerobes. Other baseline assessments included clinical signs and symptoms of the index infection, surgical wound examination, vital sign and estimation of CrCl. Hematology, chemistry, coagulation, urinalysis and direct Coombs test were done at SRL Inc. (Shinjyuku-ku, Tokyo, Japan). Blood samples for measuring drug concentration were collected at Day 1 (prior to first dose of study drug) and Day 3 and measured at MicroConstants Inc. (San Diego, California, US).

Efficacy assessments (clinical response and microbiological response) were conducted at the End-of-Therapy visit (EOT; completion of study drug administration) and the Test-of-Cure visit (TOC; Day 28 ± 2 days). All adverse events (AEs) were collected until Late Follow-up (LFU: Day 42 ± 3 days).

Bacterial species identification and antimicrobial susceptibility testing on all baseline intra-abdominal samples were performed by LSI Medience Corporation (Itabashi-ku, Tokyo, Japan) in compliance with Clinical and Laboratory Standards Institute (CLSI) standards and guidelines M07-A10 (2015), M100-S25 (2015), M45-A2 (2010) and M11-A8 (2012).

2.3. Efficacy and safety evaluation

The primary efficacy endpoint was assessed based on the clinical response. The primary efficacy analysis population for the clinical response was the clinically evaluable (CE) population, which included subjects who received study therapy for a minimum of 3 days, met the protocol-specific disease definition of cIAI, and adhered to study procedures. The efficacy analysis population for the microbiological response was the expanded microbiologically evaluable (EME) population, which included subjects who had at least 1 baseline intra-abdominal pathogen and met all CE population criteria. The primary time point for the efficacy analysis was TOC.

The primary efficacy endpoint was clinical response rate at TOC, defined as the proportion of subjects in the analysis population who have a response of clinical cure at TOC. Clinical cure was defined as complete resolution or significant improvement in signs and symptoms of the index infection, such that no additional antibacterial therapy or surgical or drainage procedure is required for the index infection. Clinical failure was defined as death due to cIAI prior to the assessment visit, persistent or recurrent infection requiring additional intervention, treatment with additional antimicrobials for ongoing symptoms of cIAI and/or surgical site infection. An indeterminate response (e.g. systemic antibiotics use for adverse event other than index infection) was excluded from the analysis if failure was not observed at the previous timepoint.

The secondary efficacy endpoints were 1) clinical response rate at EOT, 2) per-subject microbiological response rate at EOT and TOC, defined as the proportion of subjects in the analysis population who have a favorable microbiological response at the visit (favorable microbiological response was defined as microbiological eradication or presumed eradication of all pathogens isolated at baseline), 3) per-pathogen microbiological response rate at TOC, defined as the proportion of subjects in the analysis population who have an outcome of microbiological eradication or presumed eradication for each pathogen isolated at baseline. Persistence and presumed persistence were regarded as unfavorable microbiological responses (failure). An indeterminate response was excluded from the analysis if failure was not observed at the previous timepoint.

The safety evaluation was conducted in the safety population, which consists of all enrolled subjects who received at least one dose of the study medication. The primary endpoints were the proportions of subjects with all adverse events (AEs), drug-related AEs, serious AEs and serious drug-related AEs, and the proportion of subjects who discontinued due to an adverse event in the safety population.

2.4. Statistical analysis

For the primary efficacy endpoint of clinical response rate at the TOC visit, the point estimate and two-sided 95% confidence interval (CI) of response rate were calculated using the Clopper-Pearson method. For the secondary endpoints, the same method was applied as the primary endpoint. Missing data, including indeterminate responses, were handled with a data-as-observed approach (i.e. excluded from analyses if failure was not observed at the previous timepoint). The 95% confidence intervals were provided using the Clopper-Pearson method for key safety endpoints.

3. Results

3.1. Characteristics in Japanese patients

A total of 100 Japanese were enrolled into the study and received the study medication. The median duration of study treatment and number of tazobactam/ceftolozane doses were 6.5 days and 16.5 doses, respectively. Among these, 92 subjects were included in the CE population (Fig. 1).

Subject characteristics of the 100 subjects in the safety population are presented in Table 1. The proportions of male subjects was high (67%) and almost half of the subjects were ≥65 years of age and/or were renally impaired (47% and 45% respectively). The most common anatomic site of infection was the appendix (53 subjects), followed by the gallbladder (30 subjects). More than half of subjects had an intraabdominal abscess and/or peritonitis (68% and 67% respectively). Laparotomy (44%) and laparoscopy (43%) were the major types of baseline surgical intervention. The details of the major surgical intervention were appendectomy (44%), cholecystectomy (24%), only drainage (13%), intestinal resection (6%). Twenty six subjects started study treatment before the operation and most of them received only one dose of tazobactam/ceftolozane before the operation. One subject started study treatment and received one dose of tazobactam/ceftolozane during the operation. Failure of prior antibacterial therapy at baseline was not common (16%). Prior antibacterial therapies in these patients were levofloxacin (8), meropenem (3), sulbactam/cefoperazone (2), tazobactam/piperacillin (2), amoxicillin (1), cefazolin (1), ceftazidime (1), ceftriaxone (1), clarithromycin (1), flomoxef (1), metronidazole (1), ofloxacin (1) and vancomycin (1) (five subjects used more than one prior antibacterial therapy).

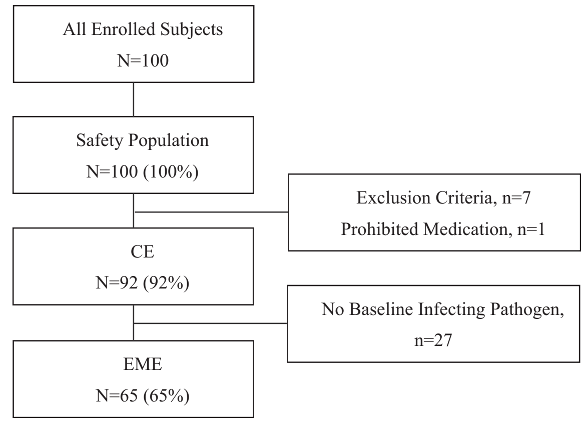

Fig. 1. Schematic of analysis populations. Japanese patients included in each analysis populations were shown as Fig. 1.

Table 1
Subject Characteristics in Japanese Patients with cIAI (Safety Population).

	n (%)
Subjects in population	100
Male	67 (67.0)
≥65 years of age	47 (47.0)
Renal impairment (30 ≤ CrCl < 80)	45 (45.0)
Baseline APACHE II score ≥ 10[a]	19 (19.0)
Anatomic Site of Infection[b]	
Appendix	53 (53.0)
Gallbladder	30 (30.0)
Colon	8 (8.0)
Liver	8 (8.0)
Stomach/Duodenum	4 (4.0)
Jejunum/Ileum	3 (3.0)
Intra-abdominal Abscess, present	68 (68.0)
Peritonits, present	67 (67.0)
Disease Status	
Subjects with a baseline intra-abdominal pathogen identified	66 (66.0)
Subjects with a polymicrobial infection	57 (57.0)
Subjects with a monomicrobial infection	9 (9.0)
Failure of prior antibacterial therapy	16 (16.0)
Type of baseline surgical intervention for cIAI	
Laparotomy	44 (44.0)
Laparoscopy	43 (43.0)

Percentages are calculated 100 x (n/number of subjects in population).
[a] APACHE II score = acute physiology score + age points + chronic health points. Minimum score = 0; maximum score = 71.
[b] Investigator may choose more than one site.

3.2. Clinical response

The number of subjects with clinical cure at the EOT and TOC visits in the CE population is presented in Table 2. TAZ/CTLZ plus metronidazole sustained a high clinical response rate up to the TOC visit (94.6% and 92.0% for EOT and TOC respectively).

The clinical response rate by disease type (the site of intra-abdominal infection at baseline) and by subgroup at the TOC is shown in Table 3. TAZ/CTLZ plus metronidazole demonstrated a favorable clinical response rate regardless of the disease type (92.3% for cholecystitis, 100% for liver abscess, 93.5% for intra-abdominal abscess and 90.2% for peritonitis) and subgroup (92.9% for ≥65 years and 88.9% for CrCl ≤50 mL/min). The clinical response rate was 100% (5/5 subjects) in the ESBL-positive *Enterobacteriaceae* subgroup. Seven subjects were regarded as clinical failure at the TOC visits due to surgical wound infections which needed additional incision and/or drainage (4), persistent cIAI (2), and recurrence of peritonitis (1). Two subjects with persistent cIAI were trending to clinical improvement but were discontinued from study therapy, one due to withdrawal of consent on Day 6 and one for meeting the CrCl criteria for study treatment discontinuation (<30 mL/min) on Day 7, respectively. Due to the limited number of clinical failures, no subject characteristics associated with clinical failure were identified.

3.3. Microbiological response

The microbiological response rates at the EOT and TOC visits in the EME population is shown in Table 4. As with the clinical response, TAZ/CTLZ plus metronidazole achieved favorable per-subject microbiological response rates at the EOT and TOC visits (93.8% and 90.2% respectively). Against the most common baseline intra-abdominal pathogens (≥10%), the per-pathogen microbiological response rates at the TOC visit were high regardless of the pathogen (90.2% for *E. coli*, 91.7% for *K. pneumoniae*, 100.0% for *Streptococcus anginosus*, 90.0% for *Streptococcus constellatus* and 95.2% for *B. fragilis*).

3.4. Safety

A summary of safety is shown in Table 5. The common AEs (incidence ≥5%) reported in this study were hepatic enzyme increased, insomnia and gastrointestinal events. With the exception of one event of moderate diarrhea, these common AEs were considered mild in intensity. The common drug-related AEs (incidence ≥2%) were aspartate aminotransferase increased (11.0%), alanine aminotransferase increased (9.0%), diarrhea (3.0%) and nausea (2.0%). All the aspartate aminotransferase increased and alanine aminotransferase increased were resolved by the EOT visit or during the study. There was no serious drug-related AE reported during the study.

Death was reported in one subject. This subject met the criterion for study treatment discontinuation (CrCl <30 mL/min) on Day 7. The subject had a complication of rectal neoplasm at baseline and was diagnosed with severe diffuse large B-cell lymphoma after study enrollment. The subject died 27 days after the last dose of the study drug. The cause of death was judged as deterioration of diffuse large B-cell lymphoma and unrelated to the study drug by the investigator.

3.5. Clinical isolates from Japanese patients

The most common baseline intra-abdominal pathogens (≥10%) were *E. coli* (41.0%) and *K. pneumoniae* (12.0%) of the gram-negative aerobes, *S. anginosus* (11.0%) and *S. constellatus* (10.0%) of the gram-positive aerobes, and *B. fragilis* (21.0%) of gram-negative anaerobes. ESBL-positive *Enterobacteriaceae* occurred in 5 (5.0%, all were *E. coli*) subjects (Table 4). Including ESBL-positive isolates, all these clinical isolates were susceptible to TAZ/CTLZ. The MIC_{50}, MIC_{90} and MIC range of the most common clinical isolates (for species with ≥10 isolates) against TAZ/CTLZ and other drugs are shown in Table 6.

4. Discussion

The design of this study was based on the U.S. FDA guidance for industry [1] and followed the guideline for the clinical evaluation of antibiotics (October 23rd, 2017) that was released by Ministry of Health, Labor and Welfare in Japan after this study completion [10]. Several features of the study design provided a rigorous evaluation of efficacy by careful selection of a complicated disease population, and primary efficacy analysis conducted after treatment was completed. The efficacy and microbiological evaluations were conducted in subjects whose source of infection was clearly identified at the time of surgical intervention since this study required inclusion of subjects who had or had plans to have surgical intervention within 24 h of the first dose of study drug, even for cholecystitis. In addition, the primary efficacy timepoint was the TOC and surgical wound infections were regarded as clinical failure in the efficacy assessment. These are in contrast to historical study in this disease conducted for older antibiotics in Japan [11].

Solomkin et al. reported the efficacy of TAZ/CTLZ in the global Phase 3 trials in non-Japanese patients with cIAI [8]. Compared with that previous report, the proportion of elderly subjects (≥65 years) and subjects with renal impairment (30 ≤ CrCl < 80) in this study were numerically higher [Japanese: 47%, non-Japanese: 23%]

Table 2
Clinical response rate at end of therapy (EOT) and test of cure (TOC) (clinically evaluable population).

	N	n (%)	95% Confidence Interval
Subjects in CE population	92		
Clinical Response Rate at EOT	92	87 (94.6)	(87.8, 98.2)
Clinical Response Rate at TOC	88	81 (92.0)	(84.3, 96.7)

N = Number of subjects included in the analysis.
n (%) = Number of subjects who have a response of clinical cure.

Table 3
Clinical response rate by disease type and subgroup at test of cure (TOC) (clinically evaluable population).

	N	n (%)	95% Confidence Interval
Subjects in CE population at TOC	88		
Disease Type			
Cholecystitis	26	24 (92.3)	(74.9, 99.1)
Liver abscess	6	6 (100.0)	(54.1, 100.0)
Intra-abdominal abscess	62	58 (93.5)	(84.3, 98.2)
Peritonitis	61	55 (90.2)	(79.8, 96.3)
Subgroup			
< 65 years of age	46	42 (91.3)	(79.2, 97.6)
≥ 65 years of age	42	39 (92.9)	(80.5, 98.5)
CrCl> 50 mL/min	79	73 (92.4)	(84.2, 97.2)
CrCl≤ 50 mL/min	9	8 (88.9)	(51.8, 99.7)
Baseline APACHE II score < 10	67	63 (94.0)	(85.4, 98.3)
Baseline APACHE II score ≥ 10	17	15 (88.2)	(63.6, 98.5)
With ESBL-negative *Enterobacteriaceae*	42	37 (88.1)	(74.4, 96.0)
With ESBL-positive *Enterobacteriaceae*	5	5 (100.0)	(47.8, 100.0)

N = Number of subjects in that specific category.
n (%) = Number of subjects who have a response of clinical cure.

Table 4
Microbiological response at end of therapy (EOT) and test of cure (TOC) (expanded microbiologically evaluable population).

	N	n (%)	95% Confidence Interval
Subjects in EME population	65		
Per-subject Microbiological Response			
Microbiological Response Rate at EOT	65	61 (93.8)	(85.0, 98.3)
Microbiological Response Rate at TOC	61	55 (90.2)	(79.8, 96.3)
Per-pathogen Microbiological Response at TOC in the common pathogens (≥5%)			
Gram-Negative Aerobes			
Escherichia coli	41	37 (90.2)	(76.9, 97.3)
Escherichia coli, ESBL positive	5	5 (100.0)	(47.8, 100.0)
Klebsiella oxytoca	5	5 (100.0)	(47.8, 100.0)
Klebsiella pneumoniae	12	11 (91.7)	(61.5, 99.8)
Pseudomonas aeruginosa	9	8 (88.9)	(51.8, 99.7)
Gram-Positive Aerobes			
Bacillus spp.	6	6 (100.0)	(54.1, 100.0)
Streptococcus anginosus	11	11 (100.0)	(71.5, 100.0)
Streptococcus constellatus	10	9 (90.0)	(55.5, 99.7)
Gram-Negative Anaerobes			
Bacteroides fragilis	21	20 (95.2)	(76.2, 99.9)
Bacteroides thetaiotaomicron	8	7 (87.5)	(47.3, 99.7)
Bacteroides spp.	7	7 (100.0)	(59.0, 100.0)

N = Number of subjects included in the analysis.
n (%) = Number of eradicated or presumed eradicated subjects.

Table 5
Summary of adverse events in Japanese Patients with cIAI (safety population).

	Overall	Drug-related[a]
	n (%)	n (%)
Subjects in population	100	100
with one or more adverse events	62 (62.0)	19 (19.0)
Adverse events (≥5%)		
Aspartate aminotransferase increased	13 (13.0)	11 (11.0)
Alanine aminotransferase increased	11 (11.0)	9 (9.0)
Insomnia	11 (11.0)	0 (0.0)
Diarrhoea	7 (7.0)	3 (3.0)
Constipation	6 (6.0)	0 (0.0)
Nausea	5 (5.0)	2 (2.0)
with serious adverse events	10 (10.0)	0 (0.0)
who died	1 (1.0)	0 (0.0)
discontinued due to an adverse event	0 (0.0)	0 (0.0)

Every subject is counted a single time for each applicable row and column.
[a] Determined by the investigator to be related to the drug.

Table 6
The susceptibility (MIC_{50}, MIC_{90} and MIC range) of the most common clinical isolates at baseline (≥10%) against TAZ/CTLZ and other drugs.

Antibiotic	N	MIC_{50} (μg/mL)	MIC_{90} (μg/mL)	Range (μg/mL)
Escherichia coli	43			
TAZ/CTLZ		0.12	0.25	0.06–0.5
PIPC/TAZ		2	2	1–8
ABPC/SBT		4	8	2–32
CPZ/SBT		0.12	2	≤0.06–16
CAZ		0.12	0.5	0.12–8
CFPM		≤0.06	2	≤0.06 – >128
CTX		≤0.06	32	≤0.06 – >128
CTRX		≤0.06	64	≤0.06 – >128
LVFX		≤0.06	8	≤0.06–64
Escherichia coli, ESBL positive	5			
TAZ/CTLZ		NA	NA	0.12–0.5
PIPC/TAZ		NA	NA	2–8
ABPC/SBT		NA	NA	8–32
CPZ/SBT		NA	NA	2–16
CAZ		NA	NA	0.5–8
CFPM		NA	NA	2 – >128
CTX		NA	NA	32 – >128
CTRX		NA	NA	64 – >128
LVFX		NA	NA	4–64
Klebsiella pneumoniae	12			
TAZ/CTLZ		0.12	0.25	0.12–0.25
PIPC/TAZ		2	4	1–4
ABPC/SBT		4	8	2–32
CPZ/SBT		0.12	0.25	0.12–1
CAZ		0.12	0.25	≤0.06–0.25
CFPM		≤0.06	≤0.06	≤0.06 – ≤0.06
CTX		≤0.06	≤0.06	≤0.06 – ≤0.06
CTRX		≤0.06	≤0.06	≤0.06–0.12
LVFX		≤0.06	0.12	≤0.06–2
Streptococcus anginosus	11			
TAZ/CTLZ		2	4	1–4
PIPC/TAZ		0.12	0.25	≤0.06–0.25
ABPC/SBT		≤0.06	0.12	≤0.06–0.12
CPZ/SBT		0.5	0.5	0.25–0.5
CAZ		2	4	1–4
CFPM		0.5	0.5	0.25–0.5
CTX		0.25	0.25	0.12–0.25
CTRX		0.25	0.25	0.25–0.5
LVFX		1	1	0.25–1
Bacteroides fragilis	22			
TAZ/CTLZ		1	4	≤0.03–8
PIPC/TAZ		0.25	0.5	≤0.06–2
ABPC/SBT		1	4	0.5–8
CPZ/SBT		2	8	1–8
CAZ		32	>128	16 – >128
CFPM		32	>128	32 – >128
CTX		16	>128	8 – >128
CTRX		32	>128	8 – >128
LVFX		2	64	1–128

The susceptibility (MIC_{50}, MIC_{90} and MIC range) of the most common clinical isolates (for species with ≥10 isolates) from baseline intra-abdominal specimens against TAZ/CTLZ and other drugs is shown. The susceptibility test was not able to be done in one out of ten *S. constellatus* and two out of six *Bacillus* spp. isolates. The MIC range (μg/mL) of less common clinical isolates (only for 5–9 isolates) was 0.12–0.12 for *K. oxytoca* (5), 0.5–1 for *P. aeruginosa* (9), ≤0.03–8 for *S. constellatus* (9), 16->64 for *Bacteroides thetaiotaomicron* (9), 1->64 for *Bacteroides* spp. (8) respectively.

and [Japanese: 45%, non-Japanese: 30%], respectively. This may reflect the epidemiology of the current aging Japanese society, and it is notable that TAZ/CTLZ demonstrated favorable efficacy in such compromised population.

TAZ/CTLZ was well tolerated and showed favorable safety characteristics. The common drug-related AEs were aspartate aminotransferase increased (11.0%) and alanine aminotransferase increased (9.0%). This trend was similar to a Phese 3 study of TAZ/CTLZ in Japanese patients with cUTI (ClinicalTrials.gov Identifier: NCT02728089). All the aspartate aminotransferase increased and alanine aminotransferase increased AEs were considered as mild in intensity and resolved by the EOT visit or during the study.

A notable result is that a high microbiological response rate and satisfactory susceptibility were confirmed in the pathogens of clinical interest such as *P. aeruginosa* and ESBL-positive *Enterobacteriaceae*. The microbiological response rate in subjects with *P. aeruginosa* and ESBL-producing *E. coli* at TOC in the EME population was 88.9% (8/9 subjects) and 100% (5/5 subjects) respectively. The MIC range of these *P. aeruginosa* and ESBL-producing *E. coli* were 0.5–1 μg/mL and 0.12–0.5 μg/mL respectively.

A limitation of this study is that the efficacy and safety of TAZ/CTLZ was not directly compared to other antibiotics due to the non-comparative study design.

In conclusion, this study clearly demonstrated favorable safety and efficacy of TAZ/CTLZ in the Japanese cIAI patient population. Of note, the study population included a high proportion of elderly and renally impaired patients, and efficacy results reflected the microbiological environment in Japan. It is expected that the TAZ/CTLZ will be one of new choices to manage the cIAI in Japanese.

Conflicts of interest

Hiroshige Mikamo has received grant support from Pfizer Japan Inc., MSD K.K., Taisho Toyama Pharmaceutical Co., Ltd., Daiichi-Sankyo Co., Ltd., Astellas Pharma Inc., Sumitomo Dainippon Pharma Co., Ltd., Shionogi & Co., Ltd., Miyarisan Pharmaceutical Co. Ltd., Meiji Seika Pharma Co., Ltd., and Fujifilm Pharma Co., Ltd. Hiroshige Mikamo has received speaker fee from Pfizer Japan Inc., MSD K.K., Daiichi-Sankyo Co., Ltd., Astellas Pharma Inc., Toyama Chemical Co., Ltd., Miyarisan Pharmaceutical Co., Ltd. and Sumitomo Dainippon Pharma Co., Ltd. Kazuteru Monden has received grant support from Pfizer Japan Inc. Kazuteru Monden, Yoshiaki Miyasaka and Tetsuya Horiuchi were study investigator. All investigators at the study sites were funded through their institution to perform the study protocol. Elizabeth G. Rhee is an employee of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, and all other authors are employees of MSD K.K.. Employees may hold stock and/or stock options in the company.

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