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Original Article

The efficacy and safety of tazobactam/ceftolozane in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection☆

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ABSTRACT

We report efficacy and safety results for a combination of a novel cephalosporin class antibiotic and a β-Lactamase inhibitor, tazobactam/ceftolozane (1:2) at a dose of 1.5 g intravenously every 8 h in Japanese patients with uncomplicated pyelonephritis and complicated urinary tract infection.

This study design was a nonrandomized, multicenter, open-label trial, and the treatment period was 7 days. Of 115 patients enrolled in this study, 114 received tazobactam/ceftolozane, and 90 were included in the efficacy analyses. Ninety-nine isolates (bacterial count $\geq 10^5$ CFU/mL) were identified by urine culture. The main baseline uropathogens were *Escherichia coli* (80 isolates), *Klebsiella pneumoniae* (8 isolates), and *Proteus mirabilis* (3 isolates). Of these, 13 isolates were ESBL-producers.

The favorable per-patient microbiological response rate at 7 days after the final administration of tazobactam/ceftolozane was 80.7% (71/88). The response rate in uncomplicated pyelonephritis was 90.0% (36/40), complicated pyelonephritis 63.6% (14/22), and complicated cystitis 80.8% (21/26). The favorable clinical response rate was 96.6% (86/89), and composite response rate (based on microbiological and clinical response) was 80.7% (71/88). The eradication rate by uropathogen was 83.5% (66/79) in *E. coli*, 42.9% (3/7) in *K. pneumoniae*, and 100% (3/3) in *P. mirabilis*.

The incidence of drug-related adverse events was 17.5% (20/114 patients). The most common drug-related adverse events were diarrhea and alanine aminotransferase increased in 5.3% (6/114 patients each). Drug-related serious adverse events and deaths were not observed.

These results support the safety and efficacy of tazobactam/ceftolozane and suggest it will be a useful treatment for uncomplicated pyelonephritis and complicated urinary tract infection.

1. Introduction

Tazobactam/ceftolozane (TAZ/CTLZ) is an antibiotic for injection where CTLZ, a novel antipseudomonal cephalosporin class antibiotic, combined with TAZ, a β-lactamase inhibitor (BLI), at a potency ratio of 1:2.

TAZ/CTLZ has the characteristics of exerting time-dependent antibacterial activity not only on gram-negative bacteria (such as

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Enterobacteriaceae including *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*) and some gram-positive bacteria (such as *Streptococcus anginosus* and *S. viridans* spp.) but also on extended spectrum β-lactamase (ESBL)-producing bacteria and drug-resistant *P. aeruginosa* [1] [2].

Outside of Japan, Phase 3 global studies for complicated urinary tract infection (cUTI) and complicated intra-abdominal infection (cIAI) (ASPECT-cUTI and ASPECT-cIAI, respectively) have been completed. Marketing approvals have been obtained in the United States (December 2014), the European Union (September 2015) and other regions. Wagenlehner et al. reported that TAZ/CTLZ demonstrated non-inferiority and superiority of efficacy in cUTI to levofloxacin in ASPECT-cUTI [3].

We report the results of a Phase 3 Japanese study (MK-7625A-014) to assess the efficacy and safety of TAZ/CTLZ in Japanese patients with uncomplicated pyelonephritis and cUTI.

2. Patients and methods

2.1. Study design and target population

This study is a multicenter, open-label, noncomparative study to assess the efficacy and safety of TAZ/CTLZ 1.5 g intravenously administered every 8 h for 7 days in Japanese patients aged at least 18 years who were diagnosed with uncomplicated pyelonephritis, complicated pyelonephritis, or complicated cystitis (target number of patients, 115) (ClinicalTrials.gov Identifier: NCT02728089). This study was conducted in a total of 46 Japanese study sites from May 2016 to September 2017.

The main inclusion criteria were pyuria (>10 WBCs/μL in unspun urine or ≥10 WBCs per high power field in spun urine), isolated uropathogens of $\geq 10^5$ CFU/mL from urine culture, and clinical signs or symptoms of UTI as below.

2.1.1. Uncomplicated or complicated pyelonephritis

As indicated by at least 2 of the following clinical signs or symptoms: a. Chills or pyrexia (oral >38.0 °C or axillary >37.5 °C); b. flank pain; c. costovertebral angle or suprapubic tenderness; d. nausea or vomiting.

2.1.2. Complicated cystitis

As indicated by at least 2 of the following clinical signs or symptoms, and 1 complicating factor.

Clinical signs or symptoms: a. Dysuria, pollakiuria, or urinary urgency; b. suprapubic or flank pain; c. costovertebral angle or suprapubic tenderness; d. chills or pyrexia (oral >38.0 °C or axillary >37.5 °C); e. nausea or vomiting.

Complicating factors: a. Males with a history of urinary retention; b. use of indwelling urinary catheter (which is scheduled to be removed during TAZ/CTLZ treatment); c. obstructive uropathy; d. functional or anatomical abnormality of the urinary tract.

Patients who met the following criteria were excluded: UTI caused only by gram-positive bacteria (TAZ/CTLZ does not adequately cover gram-positive pathogens); receipt of systemic antibacterial agents for the treatment of the current UTI within 48 h before the baseline urine specimen was obtained; receiving probenecid treatment (due to a potential drug interaction); permanent indwelling bladder catheter; urinary stent or nephrostomy; perinephric or intrarenal abscess; prostatitis; urethritis; epididymitis; ileal loop or vesico-ureteral reflux; severe impairment of renal function (creatinine clearance [CL_{CR}] <30 mL/min); or undergoing peritoneal dialysis, hemodialysis, or hemofiltration.

Administration of systemic antibiotics (excluding TAZ/CTLZ and systemic antibiotics active only against gram-positive bacteria) was prohibited during the study period.

This study was conducted by including only patients who provided written informed consent (or patient's legal representative), obtaining the approval of the institutional review board of each institution, and complying with Good Clinical Practice and Declaration of Helsinki.

2.2. Study method

Patients received intravenous administration of TAZ/CTLZ 1.5 g (TAZ 0.5 g/CTLZ 1 g) over 60 min every 8 h for 7 days (total of 21 doses). The patients with CL_{CR} of 30–50 mL/min received TAZ/CTLZ 750 mg (TAZ 250 mg/CTLZ 500 mg). Efficacy (microbiological response and clinical response) was evaluated at End-of-Therapy (EOT; day of the final administration of TAZ/CTLZ) and Test-of-Cure (TOC; 7 days after the final administration of TAZ/CTLZ). Safety evaluation was conducted until Late Follow-up (LFU; 28–35 days after the final administration of TAZ/CTLZ).

Vital signs, clinical signs and/or symptoms of UTI, and urine cultures were checked at baseline and specified evaluation points. Blood cultures were obtained only in patients diagnosed with pyelonephritis and in patients with indwelling catheters or suspected bacteremia at baseline. If the result of the blood culture was positive, it was repeated until a negative result was obtained. The bacterial count for uropathogens was determined at each study site. Bacterial strains isolated at the study site were sent to LSI Medience Corporation (Itabashi-ku, Tokyo, Japan) and were identified again in accordance with the Manual of Clinical Microbiology (10th edition) [4]. Drug susceptibility was measured in accordance with the Clinical and Laboratory Standards Institute (CLSI) M07-A10 (2015), M100-S25 (2015) and M45-A2 (2010). An ESBL-producer was defined as an isolate with MIC ≥2 μg/mL for ceftazidime or cefotaxime alone that was decreased by ≥ 8-fold for ceftazidime/clavulanic acid.

Measurements for hematology, blood biochemistry, urine, and direct Coombs test were conducted at SRL Inc. (Shinjyuku-ku, Tokyo, Japan).

2.3. Efficacy and safety evaluation

Microbiological, clinical, and composite responses were evaluated as “favorable,” “unfavorable,” or “indeterminate.” The definition for each efficacy endpoint is shown below.

2.3.1. Microbiological response

(Favorable) A urine culture shows all uropathogens ($\geq 10^5$ CFU/mL) found at baseline were decreased to $<10^4$ CFU/mL; (Unfavorable) A urine culture with $\geq 10^4$ CFU/mL of the baseline uropathogen; (Indeterminate) No available data.

2.3.2. Clinical response

(Favorable) Complete resolution of or marked improvement of all clinical signs and/or symptoms related to UTI; (Unfavorable) Persistence of clinical signs and/or symptoms related to UTI, or new signs and/or symptoms that require additional or alternative antimicrobial therapy for UTI; (Indeterminate) No available data.

2.3.3. Composite response

(Favorable) Microbiological and clinical responses are “favorable”; (Unfavorable) microbiological or clinical responses are “unfavorable”; (Indeterminate) microbiological and/or clinical responses are “indeterminate.”

Safety endpoints were set as follows: adverse events (AEs), drug-related AEs, serious AEs (SAEs), drug-related SAEs, and AEs leading to TAZ/CTLZ discontinuation. All AEs were reported by the investigator from the time of initial dose of TAZ/CTLZ through LFU

visit. A SAE is any adverse event occurring at any dose or during any use of TAZ/CTLZ that: 1) Results in death, 2) Is life threatening, 3) Results in a persistent or significant disability/incapacity, 4) Results in or prolongs an existing inpatient hospitalization, 5) Is a congenital anomaly/birth defect, 6) Is a cancer, 7) Is associated with an overdose, or 8) Other important medical events.

2.4. Statistical analysis

The primary endpoint was microbiological response in the Microbiologically Evaluable (ME) population at TOC. Secondary endpoints were clinical and composite responses (based on microbiological and clinical responses). Two efficacy analysis populations were defined as follows: The Clinically Evaluable (CE) population is the population that received TAZ/CTLZ, had an uropathogen at baseline, complied with study procedures, and can be evaluated for clinical response; The ME is a subset of the CE population that can be evaluated for microbiological response. The primary analysis populations for efficacy were CE for clinical response and ME for microbiological and composite responses. For the microbiological response, efficacy was evaluated only for gram-negative bacteria. The primary time-point for efficacy was TOC, and secondary was EOT.

Patients with missing data (including indeterminate) in each efficacy analysis were excluded from the analysis population. Also, unfavorable responses were carried forward such that all evaluations at subsequent time-points would be unfavorable. For primary and secondary endpoints, efficacy was shown by the point estimate and two-sided 95% confidence intervals of response rate (favorable/favorable + unfavorable) using the Clopper-Pearson method.

The safety analysis population was defined as the population that received TAZ/CTLZ at least once. All AEs were summarized, and the 95% confidence interval provided for safety endpoints.

3. Results

3.1. Patient populations analyzed

A total 115 patients were enrolled in this study, and 114 patients received TAZ/CTLZ. Of these patients, the following were excluded from the CE population: 19 patients because of insufficient bacterial count of uropathogen at baseline and 5 patients for noncompliance with TAZ/CTLZ administration. The CE population included 90 patients. No patient was excluded from the ME population; therefore, the CE was same as the ME population (Fig. 1).

3.2. Characteristics in patients

Table 1 shows the patient baseline demographics and disease characteristics in the CE/ME populations (n = 90). Of the patients, 70.0% (n = 63) were elderly (≥65 years) and 66.7% (n = 60) had mild to moderate renal impairment (30≤ CL_{CR} < 80 mL/min). The proportion of females was approximately twice that of male. The mean body weight was 59.9 kg. 13.3% (n = 12) had temporary catheter placement, 5.6% (n = 5) had received prior antibiotics (within 14 days before administration of TAZ/CTLZ), and 26.7% (n = 24) had concomitant bloodstream infection (bacteremia).

The most common diagnosis was uncomplicated pyelonephritis. The rate of complicated pyelonephritis was approximately the same as that of cystitis (complicated pyelonephritis 26.7% [n = 24], complicated cystitis 28.9% [n = 26]). The most common complicating factor in the complicated pyelonephritis patients was urinary calculi (nephrolithiasis 33.3% and calculus ureteric 29.2%); 45.8% of the total patients had at least 2 complicating factors. In complicated cystitis patients, the proportion of patients with neurogenic bladder dysfunction as a complicating factor was high (84.6%), and half of the total patients had at least 2 complicating factors.

At baseline, 90.0% (n = 81) of the patients had monomicrobial infections, and 10.0% (n = 9) had polymicrobial infections. The bacterial count of uropathogens was ≥10^5 to <10^6 CFU/mL in 43.3% (n = 39); ≥10^6 to <10^7 CFU/mL in 23.3% (n = 21); and ≥10^7 CFU/mL

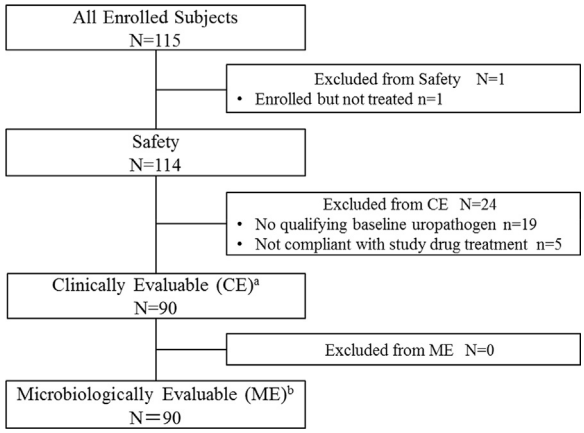

Fig. 1. Schematic of Analysis Populations.
a; The clinical response assessments included 89 patients at EOT and 89 patients at TOC, after excluding "indeterminate" patients at each time-point. b; The microbiological response assessments included 87 patients at EOT and 88 patients at TOC, after excluding "indeterminate" patients at each time-point. The composite response at TOC included 88 patients.

Table 1
Patient characteristics (CE/ME Population).

	TAZ/CTLZ (N = 90)	
	n	(%)
Gender [male/female]	31/59	(34.4/65.6)
Age (years) [mean ± SD]	[67.5 ± 14.1]	
Weight (kg) [mean ± SD]	[59.9 ± 13.8]	
Baseline creatinine clearance (mL/min) [mean ± SD]	[74.1 ± 27.0]	
Number of patients with uncomplicated pyelonephritis	40	
Number of patients with complicated pyelonephritis	24	
Complicating factors		
Calculus ureteric	7	(29.2)
Diabetes mellitus	6	(25.0)
Ureteropelvic junction obstruction	1	(4.2)
Nephrolithiasis	8	(33.3)
Neurogenic bladder dysfunction	10	(41.7)
Benign prostatic hypertrophy	8	(33.3)
Number of complicating factors		
1	13	(54.2)
≥2	11	(45.8)
Number of patients with complicated cystitis	26	
Complicating factors		
Calculus ureteric	1	(3.8)
Diabetes mellitus	3	(11.5)
Nephrolithiasis	4	(15.4)
Neurogenic bladder dysfunction	22	(84.6)
Benign prostatic hypertrophy	10	(38.5)
Renal cyst	1	(3.8)
Number of complicating factors		
1	13	(50.0)
≥2	13	(50.0)
Number of patients with bacteremia (positive blood culture at baseline)	24	(26.7)

N = Number of patients included in the analysis. n (%) = Number of patients in specific category. Percentages are calculated as 100×(n/N).

in 33.3% (n = 30). As for uropathogens at baseline (≥10^5 CFU/mL), 99 were isolated from 90 patients, and most were *E. coli* (80 isolates, including 12 ESBL-producers). The other isolated bacteria included *K. pneumoniae* (8 isolates, including 1 ESBL-producer), *P. mirabilis* (3 isolates), *Proteus vulgaris* and *Streptococcus agalactiae* (2 isolates each), and 1 isolate each of *Citrobacter koseri*, *Enterobacter aerogenes*, *P. aeruginosa* and *Corynebacterium*. In any isolated *Enterobacteriaceae* spp. including ESBL-producing strains, the range of MIC to TAZ/CTLZ was 0.06–0.5 μg/mL; *P. aeruginosa* MIC was 0.5 μg/mL (Table 2). All the gram-negative bacteria isolated as uropathogens were susceptible to TAZ/CTLZ. 24 strains were isolated from blood culture. These included 18 *E. coli* (including 1 ESBL-producer), 4 *K. pneumoniae*, and 1 *P. vulgaris* and 1 *Staphylococcus capitis*. In most cases, the bacterium isolated from urine culture was the same strain as that isolated from blood culture.

3.3. Efficacy

3.3.1. Microbiological response

In the ME population, the microbiological response assessments included 87 patients at EOT and 88 patients at TOC, after excluding "indeterminate" patients at each time-point.

The favorable microbiological response rate at TOC was 80.7% in 88 patients. All patients had a favorable microbiological response at EOT. Approximately 20% of the patients experienced recurrence of uropathogens at baseline (≥10^4 CFU/mL) during the period between EOT and TOC (Fig. 2). The bacterial species that recurred were *E. coli* (13 isolates) and *K. pneumoniae* (4 isolates), which included 8 ESBL-producers (7 *E. coli* and 1 *K. pneumoniae*). All these strains with the exception of the 1 *E.coli* strain missing data at TOC were sensitive to TAZ/CTLZ.

Microbiological response rates by diagnosis at TOC tended to be lower when complicating factors were present, particularly for upper UTI (uncomplicated pyelonephritis 90.0%, complicated cystitis 80.8%, and complicated pyelonephritis 63.6%) (Table 3). Among 23 patients with at least 2 complicating factors for efficacy analysis, the efficacy of TAZ/CTLZ was 78.3%. The response rate was high in the elderly aged ≥75 years, and no difference in response rate due to gender was observed. Although few patients already had an indwelling catheter at baseline, TAZ/CTLZ was effective in all patients. The response rate in the patients with bacteremia was similar to that in the patients without bacteremia (bacteremia: 78.3%, non-bacteremia: 81.5%). Of the patients with bacteremia (n = 23), 22 had negative blood cultures by TOC. Patients with the highest bacterial counts of the uropathogen at baseline (≥10^7 CFU/mL) had a slightly lower favorable response.

The eradication rate by uropathogen at TOC was 83.5% in *E. coli*. Although the number of strains was limited, the microbiologic response was favorable in all strains of other gram-negative bacteria except for *K. pneumoniae* (*C. koseri*, *E. aerogenes*, *P. mirabilis*, *P. vulgaris*, and *P. aeruginosa*). The response rate remained at 42.9% in *K. pneumoniae* (Table 4). The response rate in 13 ESBL-producing strains was low at approximately 1/2 times of that of non-ESBL-producers.

3.3.2. Clinical response and composite response

In the CE population, the clinical response assessments included 89 patients at EOT and 89 patients at TOC, after excluding "indeterminate" patients at each time-point. The favorable clinical response rate at TOC was 96.6%. Thus, study treatment was effective in nearly all of the patients. This showed that the clinical response of TAZ/CTLZ was maintained from EOT to TOC (Fig. 2).

In the ME population, the composite response at TOC included 88 patients. The favorable composite response rate was 80.7% (n = 71). TAZ/CTLZ showed both microbiologically and clinically effective in most patients.

3.4. Safety

The Safety population included 114 patients. The incidence of AEs was 58.8% (n = 67), and the incidence of drug-reaction AEs was 17.5% (n = 20). The most common drug-related AEs (incidence ≥2%) included diarrhea and alanine aminotransferase increased in 5.3% each, and aspartate aminotransferase increased in 3.5% (Table 5).

The incidence of SAEs was 11.4% (n = 13, 15 events); all SAEs were assessed as unrelated to TAZ/CTLZ by the investigator. Drug-related SAEs and deaths were not observed.

AEs leading to TAZ/CTLZ discontinuation were observed in 2 patients, one patient with moderate headache and the other with mild hepatic function abnormal. Both events were non-serious and resolved after the discontinuation of TAZ/CTLZ, but assessed as related to TAZ/CTLZ by the investigator.

Table 2
MICs (μg/mL) of TAZ/CTLZ for baseline uropathogens (CE/ME population).

Baseline uropathogen	TAZ/CTLZ (N = 90)		
	N1	MIC range (μg/mL)	MIC_{90} (μg/mL)
Gram-Negative Aerobes			
Citrobacter koseri	1	0.12–0.12	
Enterobacter aerogenes	1	0.12–0.12	
Escherichia coli	80	0.06–0.5	0.25
Escherichia coli (ESBL+)	12	0.12–0.5	0.25
Klebsiella pneumoniae	8	0.06–0.5	
Klebsiella pneumoniae (ESBL+)	1	0.12–0.12	
Proteus mirabilis	3	0.25–0.25	
Proteus vulgaris	2	0.25–0.5	
Pseudomonas aeruginosa	1	0.5–0.5	
Gram-Positive Aerobes			
Corynebacterium	1	≤0.03–≤0.03	
Streptococcus agalactiae	2	0.25–0.5	

N1 = Number of uropathogens with baseline MIC data available. MIC = Minimum inhibitory concentration. MIC_{90} = Minimum inhibitory concentration required to inhibit the growth of 90% of organisms. Patients with more than one uropathogen isolated at baseline are counted only once in the overall population N, but counted as multiple within each uropathogen.

4. Discussion

In Japan, total bacterial count including all uropathogens has been used conventionally as an index of microbiological response in the development of antibiotics against UTI. However, this study evaluated the efficacy of TAZ/CTLZ by bacterial count of each uropathogen. By using per-uropathogen microbiological response, the drug efficacy for UTI can be accurately evaluated. This evaluation method is also based on the microbiological evaluation index recommended in "Japanese guideline for clinical research of antimicrobial agents on urogenital infections: Second edition" [5] and Guidance for Industry "cUTIs: Developing Drugs for Treatment (2015)" [6].

In microbiological response assessment, this study set the bacterial count for favorable microbiological response as <10^4 CFU/mL, which is higher than has been applied in prior antibiotic studies in this indication. When the prior standard bacterial count, which was considered to be microbiologically effective (<10^3 CFU/mL) and recommended by the guideline on the evaluation of medicinal products (2013) [7] was applied, the favorable microbiological response rate was shown to be 78.4% (69/88 patients), which was not largely different from that when the currently applied standard of <10^4 CFU/mL was used. In the present study, at TOC, baseline

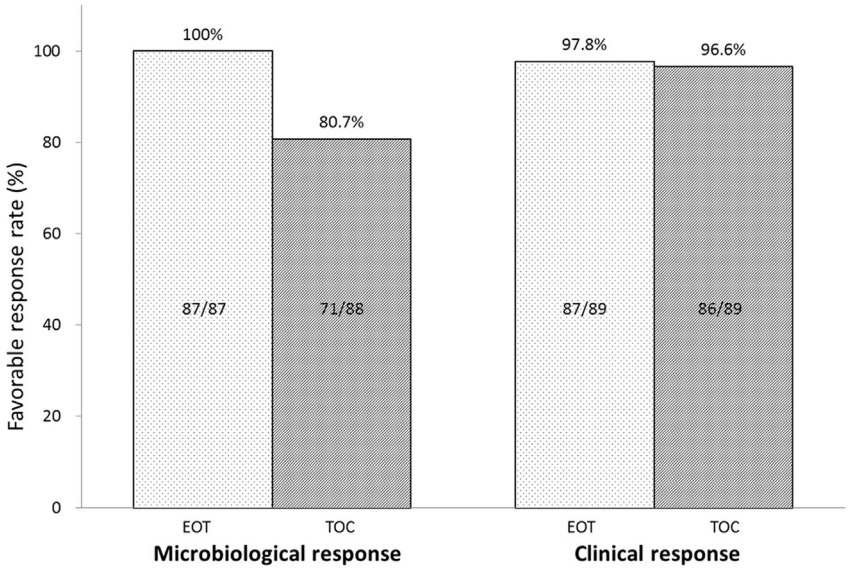

Fig. 2. Favorable microbiological response and favorable clinical response at end of therapy (EOT), and test of cure (TOC) (CE/ME Population).
(%) = Number of patients with favorable response/Number of patients included in the analysis.

Table 3
Per-patient microbiological response at test of cure (TOC) by subgroups (ME Population).

Subgroup (patient profiles at baseline)		TAZ/CTLZ (N = 88)	
		n/N1	(%)
Diagnosis	Uncomplicated pyelonephritis	36/40	(90.0)
	Complicated pyelonephritis	14/22	(63.6)
	Complicated cystitis	21/26	(80.8)
CL_{CR} (mL/min)	≤50	7/10	(70.0)
	>50	64/78	(82.1)
Age (years)	18 to 64	20/27	(74.1)
	65 to 74	26/33	(78.8)
	≥75	25/28	(89.3)
Gender	Male	25/30	(83.3)
	Female	46/58	(79.3)
Presence of bacteremia (patient with positive blood culture)	Yes	18/23	(78.3)
	No	53/65	(81.5)
Patient with/without indwelling catheter	With	10/10	(100.0)
	Without	61/78	(78.2)
Patient with/without nephrolithiasis or calculus ureteric as complicating factors	With	9/16	(56.3)
	Without	26/32	(81.3)
Number of complicating factors for complicated urinary tract infection	1	17/25	(68.0)
	≥2	18/23	(78.3)
Number of uropathogens present	1	66/83	(79.5)
	2	4/4	(100.0)
	≥3	1/1	(100.0)
Bacterial counts of uropathogen (CFU/mL)	$\geq 10^5$, $<10^6$	32/39	(82.1)
	$\geq 10^6$, $<10^7$	18/21	(85.7)
	$\geq 10^7$	21/28	(75.0)
Prior treatment with antimicrobial agents (within 14 days)	With	3/5	(60.0)
	Without	68/83	(81.9)

N = Number of patients included in the analysis. N1 = Number of patients within a specific category.
n (%) = Number of patients who have per-patient microbiological response of success.
Percentages are calculated as 100 × (n/N1).

uropathogen were isolated from urine cultures in 19 patients. The distribution of bacterial count of uropathogens was 10^3 CFU/mL (2 patients), 10^4 CFU/mL (6 patients), 10^5 CFU/mL (4 patients), 10^6 CFU/mL (1 patients), and 10^7 CFU/mL (6 patients). Most isolated bacterial counts were quantitatively $\geq 10^4$ CFU/mL.

This study design was similar to that of the ASPECT-cUTI study conducted outside Japan. The results demonstrate similar effectiveness in microbiological, clinical, and composite responses as those reported in the ASPECT-cUTI study by Wagenlehner et al. (favorable response rate [MK-7625A-014 vs. ASPECT-cUTI]: microbiological response [80.7% vs. 86.2%], clinical response [96.6% vs. 95.9%], and composite response [80.7% vs. 83.3%]).

When pyelonephritis occurred, the complication of bloodstream infection tends to occur by tissue destruction spreading from collecting kidney tubules to renal parenchyma. As specified by the protocol, blood cultures were obtained at baseline mainly in

Table 4
Per-pathogen microbiological response of baseline uropathogens at test of cure (TOC) (ME Population).

Baseline Uropathogens	Favorable response[a] (%)	
Escherichia coli	66/79	(83.5)
Escherichia coli (ESBL+)	5/12	(41.7)
Klebsiella pneumoniae	3/7	(42.9)
Klebsiella pneumoniae (ESBL+)	0/1	(0.0)
Proteus mirabilis	3/3	(100)
Proteus vulgaris	2/2	(100)
Citrobacter koseri	1/1	(100)
Enterobacter aerogenes	1/1	(100)
Pseudomonas aeruginosa	1/1	(100)
Total	77/94	(81.9)

Eradication: the bacterial count of baseline uropathogen was $<10^4$ CFU/mL at TOC.
Persistence: the bacterial count of baseline uropathogen was $\geq 10^4$ CFU/mL at TOC.
[a] Favorable response = Eradication/(Eradication + Persistence).

Table 5
Patients with adverse events -overall and drug-related (incidence of adverse events ≥ 2%) in treatment period and follow-up days (Safety population).

	TAZ/CTLZ (N = 114)			
	Overall		Drug-related[a]	
	n	(%)	n	(%)
Diarrhea	9	(7.9)	6	(5.3)
Alanine aminotransferase increased	9	(7.9)	6	(5.3)
Constipation	9	(7.9)	1	(0.9)
Aspartate aminotransferase increased	7	(6.1)	4	(3.5)
Insomnia	5	(4.4)	0	(0.0)
Headache	4	(3.5)	1	(0.9)
Pyelonephritis	4	(3.5)	0	(0.0)
Pyelonephritis acute	4	(3.5)	0	(0.0)
Contusion	4	(3.5)	0	(0.0)
Viral upper respiratory tract infection	3	(2.6)	0	(0.0)

[a] Determined by the investigator to be related to the drug. Every patient is counted a single time for each applicable row and column. A specific adverse event appears on this report only if its incidence in one or more of the columns meets the incidence criterion in the report title, after rounding.

pyelonephritis patients. Of the 67 patients who underwent blood culture, 24 patients had a positive blood culture, which showed that 1 in 3 patients with pyelonephritis concomitantly experienced bacteremia.

Of 23 patients with concomitant bacteremia (except for 1 patient whose microbiological response at TOC was “indeterminate,”) the eradication of uropathogen in urine culture was observed in 18 patients at TOC, and almost all patients (22 patients) had negative blood cultures by TOC. The high response rate (78.3%) in patients with severe UTI complicated by bloodstream infection demonstrates the promising utility of TAZ/CTLZ as an effective therapeutic drug for UTI.

The isolation rate of ESBL has been increasing year by year in Japan [8]. This drug is a combination antibiotic with TAZ, a BLI. In ASPECT studies, high clinical cure rates with TAZ/CTLZ treatment of cIAI and cUTI caused by ESBL-producing *Enterobacteriaceae* was demonstrated [9]. All ESBL-producing strains isolated in this study were susceptible to TAZ/CTLZ; therefore, a favorable efficacy response to TAZ/CTLZ treatment was expected. However, the favorable microbiological response rate in patients with isolated ESBL-producing strains remained at 38.5% (5/13 patients). 8 patients with unfavorable response had high bacterial counts for baseline uropathogen (10^7 CFU/mL in 6 patients), and 7 patients had cUTI, of whom 4 patients had 2 or 3 complicating factors and 6 patients had concomitant diabetes mellitus. There were comorbidities or baseline disease characteristics associated with poorer response that may have contributed to the observed efficacy in these patients.

The microbiological response rate for *K. pneumoniae* was numerically lower than that of other strains. However, all *K. pneumoniae* isolates were susceptible, with low MIC values. Since there were only a few patients (7 patients) in which *K. pneumoniae* was isolated, it is difficult to determine the reason why the response rate was low.

This paper includes the following limitations: Because of the open-label, noncomparative design of this study, it cannot be directly compared with existing therapeutic drugs for UTI. Also, this study with approximately 100 patients includes uncomplicated pyelonephritis and cUTI (including upper and lower UTI), thus, the number of the patients in each disease is limited, and may affect generalization of the results.

In conclusion, microbiological and clinical effectiveness of TAZ/CTLZ were clearly demonstrated in uncomplicated pyelonephritis and cUTI. In addition, TAZ/CTLZ was generally safe and well-tolerated. In the future, the aging population in Japan may be accompanied by a rapid increase in morbidity and recurrence rates of UTI because of increases in concomitant diseases (which can be a complicating factor for UTI) and because of the effects of decrease in physiological function associated with aging. Moreover, there is concern for increases in antibiotic-resistant bacteria, such as ESBL-producing strains and drug-resistant *P. aeruginosa*.

TAZ/CTLZ is a novel antibiotic with excellent antibacterial activity against gram-negative bacteria such as *Enterobacteriaceae*, including ESBL-producing strains and drug-resistant *P. aeruginosa*, and a favorable safety profile. The results of this study support that TAZ/CTLZ will be expected as a new option in antibiotic treatment in Japanese patients with uncomplicated pyelonephritis and cUTI.

Conflicts of interest

Soichi Arakawa has received speaker fee from Taisho Toyama Pharmaceutical Co., Ltd. Soichi Arakawa was a coordinating investigator in MK-7625A-014 study. Kazuya Kawahara has none declared. Kazuya Kawahara was investigator in MK-7625A-014 study. Motoshi Kawahara has none declared. Motoshi Kawahara was investigator in MK-7625A-014 study. Mitsuru Yasuda has received grant support from Astellas Pharma Inc., Ono Pharmaceutical Co., Ltd., GlaxoSmithKline K.K., Daiichi Sankyo Co., Ltd., Takeda Pharmaceutical Co., Ltd., and Novartis Pharma K.K. Mitsuru Yasuda was investigator in MK-7625A-014 study. 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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