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Original Article

Pharmacokinetic-pharmacodynamic comparison of ceftriaxone regimens in acute cholangitis☆

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ABSTRACT

The most important factors determining the prognosis of patients with acute cholangitis (AC) are prompt biliary drainage and appropriate choice of antibiotics. This study was performed to evaluate whether dividing the number of doses based on the PK-PD theory contributes to better clinical outcome in the management of acute cholangitis. We measured ceftriaxone levels in blood and bile in 21 cases diagnosed with moderate-to-severe AC. Eleven cases were administered 2 g of ceftriaxone once-daily (group A) and 10 cases were given 1 g of ceftriaxone twice-daily (group B). The theoretical effect of ceftriaxone was evaluated by pharmacokinetic–pharmacodynamic (PK–PD) parameters. Clinical efficacy was evaluated by body temperature, white blood cell count and serum levels of C-reactive protein. Minimum level of ceftriaxone in serum (in mg/L) in groups A and B at 24 h after the first dose was 9.1 and 9.2, whereas that in bile was 2.9 and 2.5, respectively. The minimum inhibitory concentration (MIC) of ceftriaxone for all isolated bacteria was below the minimum serum and biliary concentration of ceftriaxone 24 h after the first administration (except for *Enterococcus* species). The MIC for isolated bacterial strains was <16 mg/L, which is the PK–PD breakpoint for ceftriaxone at 2 g/day. Both regimens showed clinical efficacy and did not contradict the effect predicted based on PK–PD.

1. Introduction

Acute cholangitis (AC) is a bacterial infection of the biliary tract that results from a combination of bactibilia and biliary obstruction. AC leads to entry of bacteria and/or endotoxins into the bloodstream [1]. AC can be life-threatening despite advances in treatment, and mortality of 4%–10% has been reported [2]. Therefore, timely biliary drainage and administration of appropriate antibiotics are important to obtain a better prognosis in AC patients [3–6]. In general, antibiotics with a low minimum inhibitory concentration (MIC; an indicator of the potency of antibiotic activity) are selected. Furthermore, the tissue transferability and pharmacokinetics (PK) of antibiotics greatly affect efficacy. PK parameters include bioavailability, maximum drug concentration in serum, elimination half-life, and area under the drug–response curve following dosing. Recently, it has become evident that pharmacodynamic (PD) characteristics also contribute to determination of administration schedules. For mild cases of AC, Tokyo Guidelines (TG) 07 and 18/13 for AC recommend administration of antibiotics with a broad spectrum of activity against the expected causative bacteria [2,7]. AC is often caused by infection with a single intestinal bacterial species, such as *Escherichia coli*. However, in clinical practice, antibiotics are often administered before identification of the causative bacteria. For moderate-to-severe AC, TG07 and 18/13 recommend use of broad-spectrum penicillin and second-generation cephem antibiotics as first-line treatment. For cases with severe infection involving multiple drug-resistant pathogens, TG07 and 18/13 recommend administration of third- or fourth-generation cephem antibiotics (which have a broad antimicrobial spectrum) as first-line treatment. After the causative bacteria has been identified, antibiotics targeting them should be chosen. New quinolones and carbapenems have been recommended as second-line treatment if first-line treatment is ineffective, and monobactams are recommended if Gram-negative bacteria are detected [2–5,8,9]. The clinical efficacy of antibiotics is influenced not only

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by the drug concentration in serumbut also by tissue transferability. Antibiotics migrate from peripheral blood into tissues and are excreted from tissues to peripheral blood. Therefore, measurement of the drug concentration in serum alone cannot be used to predict the efficacy of antibiotics [9,10]. Ceftriaxone is a third-generation cephem antibiotic. Ceftriaxone exerts strong antimicrobial activity and has a broad antimicrobial spectrum for bacteria causing biliary-tract infections. However, little is known about PK–PD-based ceftriaxone treatment for AC. Here, we compared the clinical efficacy of once-daily administration of ceftriaxone (2 g) and twice-daily administration of ceftriaxone (1 g) in AC patients. We investigated the PK–PD of ceftriaxone in both treatment regimens by measurement of serum and bile concentrations of ceftriaxone.

From the viewpoint of PK-PD, β-lactams (penicillin, cephem, carbapenem) are considered to increase their clinical effectiveness by increasing the number of administrations. This study was performed to evaluate that based on the PK-PD theory to clarify whether differences in the clinical efficacy will occur by dividing the number of doses even if the daily dose is the same, and to consider the administration strategy of the antibiotic for acute cholangitis.

2. Patients and methods

2.1. Patients

The study protocol was approved by the Ethics Committee of Kyorin University Hospital (number 434; Tokyo, Japan). Twenty-one patients diagnosed with moderate-to-severe AC according to TG07 [2] in Kyorin University Hospital from October 2008 to December 2009 formed the retrospective study. Patients had to meet the following criteria: (i) endoscopic nasobiliary drainage (ENBD) was done before antibiotic administration; (ii) patients had not undergone endoscopic sphincterotomy previously; (iii) bile samples were collected 2 h and 24 h after ENBD. Twelve patients were administered 2 g of ceftriaxone once-daily (group A) and 11 cases were given 1 g of ceftriaxone twice-daily (group B). Hematologic tests and blood cultures were carried out before administration of any antibiotic. Bile was collected immediately after cannulation of the bile duct. Then, an ENBD tube was placed in the bile duct, immediately followed by ceftriaxone administration. Two hours and 24 h after ceftriaxone administration, hematologic tests were conducted, and bile samples were collected from the ENBD tube for culturing and measurement of the serum and bile concentrations of ceftriaxone (Fig. 1). The MIC for bacterial isolates was measured in the 21 patients. The ceftriaxone concentration in serum and bile was also measured and compared, and verified using PK–PD. MIC was measured by broth microdilution method of Clinical and Laboratory Standards Institute (CLSI) criteria. “Clinically effective” was identified if the body temperature decreased to 37 °C and the white blood cell (WBC) count became normal (<8600/μL). CTRX was administered until the physician judged “clinically effective”.

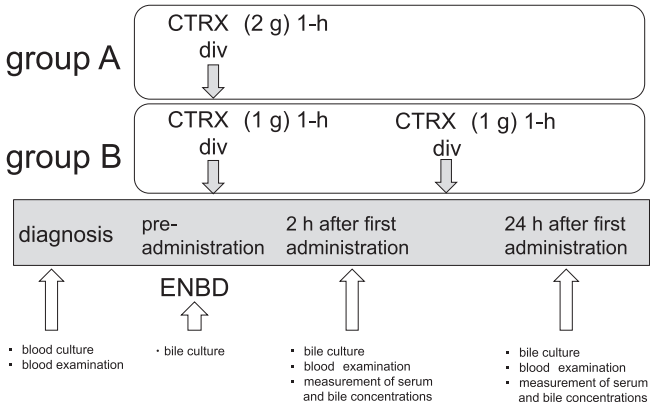

Fig. 1. Protocol of administration of CTRX *group A*: 2 g of CTRX once-daily, *group B*: 1 g of CTRX twice-daily*CTRX*: ceftriaxone, *ENBD*: Endoscopic nasobiliary drainage.

2.2. Evaluation of clinical efficacy

Body temperature was measured every 8 h after ENBD for assessment of treatment efficacy. The MIC for bacterial isolates was measured in the 21 patients, the PK-PD breakpoint tested, and the theoretical clinical efficacy determined according to the clinical course of patients. The patients survival on 30 days after treatment were evaluated.

2.3. Measurement of serum and biliary concentrations of ceftriaxone

Serum and biliary levels of ceftriaxone were measured 2 h and 24 h after the first administration of ceftriaxone. The ceftriaxone concentration in serum and bile was measured using high-performance liquid chromatography at the Institute of Applied Medicine Inc. (Sapporo, Japan). The HPLC conditions were as follows: The mobile phase consisting of acetonitrile/50 mmol/L ammonium formate (86:14) was sent to the analytical column ZIC-HILIC (2.1 × 100 mm, 5 μm, SeQuant)kept at 45 °C at a flow rate of 0.5 mL/min. The measurement wavelength of ultraviolet absorptiometer (2487, Waters Co., Ltd.) was set to 280 nm. The ceftriaxone concentration in blood and bile was measured according to the measurement method validated in “Validation test of ceftriaxone concentration in human serum (Test No. AM-MV-768) and bile (Test No. AM-MV-767) by high performance liquid chromatography ”. When the concentration was below the limit of quantification (0.2 mg/L), it was expressed as < LOQ.

2.4. Bacterial culture

Bacteria in blood and bile were cultured to investigate the susceptibility of ceftriaxone against bacterial isolates. Chocolate/sheep blood medium (Nikken Biomedical Laboratory, Kyoto, Japan) and chromID™ CPS™ Medium (Sysmex-bioMérieux, Lyon, France) were used for blood cultures. Sheep blood agar medium M58 (Eiken Chemicals, Tokyo, Japan) and Drigalski lactose agar medium (Nissui Pharmaceuticals, Tokyo, Japan) were used for bile cultures.

2.5. Statistical analyses

Results are shown as the median and range. The prevalence of fever and abnormal WBC counts in patients were calculated using the Kaplan–Meier method and compared using the log rank test. Differences between unpaired continuous or discontinuous variables between two groups were analyzed by the Student's *t*-test or χ^2 test. $p < 0.05$ was considered significant. Statistical calculations were conducted using JMP v13.0.0 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Characteristics of patients

The mean age of group-A patients was 71 (48–82) years and that of group-B patients was 68 (45–83) years. The male-to-female ratio was 7:4 and 6:4 in groups A and B, respectively. In group A and group B, respectively: four cases and six cases had an underlying

malignant tumor; one case and two cases had bacteremia; two cases and three cases had severe AC (Table 1). AC severity at the time of the diagnosis was also documented. One patient in group A and group B had severe AC, respectively. Ten patients in group A and nine patients in group B had moderate AC. Thereafter, among 19 patients with moderate AC, blood culture revealed bacteremia in three patients (one in group A and two in group B).

Urinary albumin determination has not been evaluated, and accurate assessment of renal function is difficult. The number of cases according to the eGFR classification is 3 cases in G1, 7 cases in G2 and 1 case in G3a, the average value of eGFR is 90.0 ± 11.9. mL/min/1.73 m 2 in group A, and 2 cases in G1, 7 cases in G2, 1 case in G3a, average value of eGFR is 86.8 ± 60.6 mL/min/1.73 m 2 in Group B, both groups have normal to mild renal dysfunction cases. The comparison also showed no significant difference between the two groups (p = 0.85).

Eventually, two patients in group A and three patients in group B were judged to have severe AC, and nine patients in group A and seven cases in group B were judged to have moderately severe AC. There was no significant difference in AC severity between the two groups (p = 0.52). AC severity was assessed again according to TG18/13 [2,7]: four, four, and three patients in group A, and three, six, and one patient in group B had mild, moderate, and severe AC, respectively (Fig. 2).

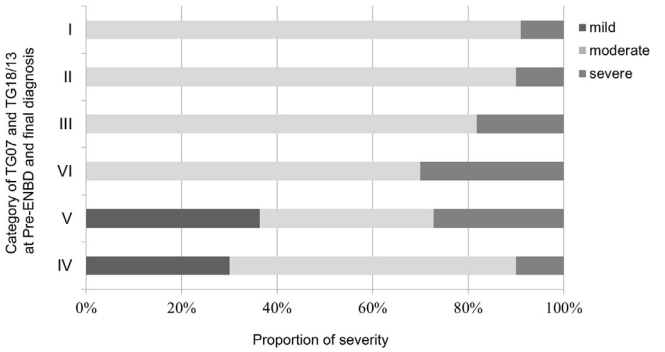

Fig. 2. Proportion of severity based on Tokyo Guideline 2007 and 2018/2013 in each. Groups. Category: I. group A (TG07) at Pre-ENBD, II. group B (TG07) at Pre-ENBD, III. group A (TG07) at Final diagnosis, VI. group B (TG07) at Final diagnosis, V. group A (TG18/13) at Pre-ENBD, IV. group B (TG18/13) at Pre-ENBD.

3.2. Bacterial isolation

Seventeen species and 44 strains of pathogenic microorganisms were isolated from bile in groups A and B. With respect to the pathogenic microorganisms isolated from bile, the percentage of patients with Gram-negative bacterial infection was 53.8% (7/13 strains) and Gram-positive bacterial infection was noted in 38.5% (5/13 species) in group A. *Candida albicans* was detected in one patient from group A. The percentage of patients with Gram-negative bacterial infection was 48.4% (15/31 strains) and Gram-positive bacterial infection was noted in 51.6% (16/31 strains) in group B. In particular, the proportion of patients with infection caused by Gram-positive bacteria, such as *Streptococcus* species and *Enterococcus* species, tended to be higher in group B. Most bacterial strains isolated from bile overlapped in the two groups. Seven species and 10 strains of pathogenic microorganisms were isolated from blood in groups A and B. Among the species isolated from blood, *Enterobacter cloacae*, *Streptococcus salivarius*, and *E. coli* were also detected in the bile of the same patients, while the other species were isolated only from blood. Of the 16 bacterial species that were isolated from the bile and whose genus was identified, nine species with two or more isolated strains were used to measure the MIC of ceftriaxone. Ceftriaxone had an MIC of ≤0.06 mg/L to 4 mg/L against six species, which showed the strong antimicrobial activity of this drug. These results showed that ceftriaxone-resistant Gram-negative bacteria, such as *E. coli* and *Klebsiella* species with AmpC β-lactamase or CTX-M-type β-lactamase, were not isolated in our study. Conversely, three species for which the use of ceftriaxone has not been approved in Japan (*Aeromonas*, *Enterococcus*, and *Pseudomonas aeruginosa*) showed a MIC of 0.12–128 mg/L (Table 2).

Table 1
Patient characteristics.

	GroupA	GroupB	p value
Number	11	10	
Gender, number (%)			0.87
Male	7 (33.3%)	6 (28.6%)	
Female	4 (19.0%)	4 (19.0%)	
Age (year), median (range)	71 (48–82)	68 (45–83)	0.50
eGFR (mL/min/1.73m2), average	90.0 ± 11.9	86.8 ± 60.6	0.85
Malignancy, number (%)			
Yes	4 (19.0%)	6 (28.6%)	
No	7 (33.3%)	4 (19.0%)	
Bacteremia, number (%)	1 (4.8%)	2 (9.5%)	0.76
Severe cholangitis [a]	2 (9.5%)	3 (14.3%)	0.94

Group A 2 g of ceftriaxone once-daily, *group B* 1 g of ceftriaxone twice-daily. Comparisons between groups were done using $\chi 2$ test. $p < 0.05$ was considered significant.

[a] Evaluation method is Criterion of severity is based on Tokyo Guidelines 2017.

3.3. MIC of ceftriaxone for strains isolated from serum and bile

The ceftriaxone concentration in serum 24 h after administration was 9.1–169.3 (median, 20.3) mg/L in group A, and 9.2–94.4 (median, 30.5) mg/L in group B. The ceftriaxone concentration in bile 24 h after its administration in groups A and B was 2.9–209.8 (median, 15.1) and 2.5–440.9 (median, 12.6) mg/L, respectively. The MIC for seven of eight bacterial species (excluding *Enterococcus* species) was lower than the minimum concentration of ceftriaxone in serum (9.1 mg/L) 24 h after drug administration in both groups. The MIC for six bacterial species (excluding *Enterococcus* species and methicillin-sensitive *Staphylococcus aureus*) was lower than the minimum concentration of ceftriaxone in bile (2.5 mg/L) 24 h after drug administration in both groups (Fig. 3).

Cause bacterial strains was defined as over 1×10^5 CFU/mL, and nine bacterial species corresponded. Of these, MIC of seven species, except for Enterococcus species and *P. aeruginosa*, were below PK-PD breakpoint [11].(Fig. 4).

3.4. Clinical course of patients

The median of administration of CTRX was 4 days with an average of 4 ± 2 days. The mean time to defervescence to ≤37 °C after the start of ceftriaxone administration was 9 ± 13 h in group A and 21 ± 39 h in group B, with no significant difference between these two groups (p = 0.43) (Fig. 5). The mean time needed to recover to a normal WBCcount was 10 ± 16 h in group A and 30 ± 50 h in group B, with no significant difference between these two groups (p = 0.34). The maximum time required for a normal WBC count was 126 h, which was observed in one patient in group B (Fig. 5). The response in both groups was 100%. Adverse events were assessed according to the criteria for adverse events set by the Japanese Society of Chemotherapy [12,13]. There were no significant adverse events of ceftriaxone in any of the 21 patients. In this study, the survival rate at day 30 was 100%.

Table 2
Breakdown of type of isolated clinical pathogens from bile (a), blood (b) and MIC range of CTRX in isolated strains (c). group A 2 g of ceftriaxone once-daily, group B 1 g of ceftriaxone twice-daily.

Pathogens (Bile)	Group A	Group B	Total
(a)			
Streptococcus spp	1	5	6
Enterococcus spp	1	5	6
Klebsiella spp	2	3	5
Escherichia coli	2	3	5
Gram-positive rods		3	3
Enterobacter cloacae		3	3
Staphylococcus aureus (MSSA)	1	1	2
Aeromonas spp	1	1	2
Anaerobic Gram (−) rods		2	2
Anaerobic Gram (+) cocci	1	1	2
Citrobacter spp	1	1	2
Bacillus spp	1		1
Candida albicans	1		1
Clostridium perfringens		1	1
Prevotella spp		1	1
Proteus mirabilis	1		1
Pseudomonas aeruginosa		1	1
Total	13	31	44
Bacteria proved by species	11	25	36
Gram-Negative bacteria	7	15	22
Gram-Positive bacteria	5	16	21
CTRX approved Pathogens	4	6	10
CTRX non-approved Pathogens	7	19	26
Pathogens (Blood)	Group A	Group B	Total
(b)			
Escherichia coli		3	3
Candida albicans		2	2
Staphylococcus epidermidis	1		1
Streptococcus salivarius group	1		1
Acinetobacter species		1	1
Klebsiella oxytoca		1	1
Enterococcus species		1	1
Total	2	8	10
Bacteria proved by species	2	6	8
CTRX approved Pathogens	2	5	7
CTRX non-approved Pathogens	0	1	1
Isolated clinical pathogens			CTRX
(c)			
Citrobacter spp			0.12
Enterobacter spp			0.12–0.25
Escherichia coli			≦0.06
Klebsiella spp			≦0.06–0.12
Streptococcus species			≦0.06–0.12
Staphylococcus aureus (MSSA)			4
****Enterococcus faecalis*			128~>128
****Aeromonas* spp			0.12
**P.aeruginosa			16
**Off-label pathogens of CTRX			CTRX:ceftriaxone

4. Discussion

Three patients were deemed to have moderate AC during the initial diagnosis, but it was found to be bacteremia which, ultimately, became a diagnosis of severe AC. Thus, it is necessary to not only carry out biliary drainage, but also to administer antimicrobial agents for moderate AC. Antibacterial agents must have a broad antibacterial spectrum and strong antibacterial effect. PK must also be considered for treatment of bacterial infections. The percentage of time spent above the MIC (%TAM) is another important feature of β-lactam antibacterial agents. Ceftriaxone is a third-generation cephem antibiotic that was developed by Hoffmann-La Roche in Switzerland. Ceftriaxone exerts strong antimicrobial activity and shows a broad antimicrobial spectrum to cover *E. coli* and Klebsiella species (which account for 40% of all the bacteria causing biliary-tract infections) as well as Serratia and Haemophilus species; it is stable against β-lactamase [14–16]. It has the longest serum half-life in clinical cases (≈8 h) among cephem antibiotics [17,18]. Often, the blood concentration of antibiotics is measured to predict efficacy of antibiotics. The concentration of antibiotics in the tissue in target organs also affects their clinical efficacy. We measured the serum and bile concentration of ceftriaxone to investigate the correlation between them. We showed that the maximum time to defervescence to ≤37 °C after ceftriaxone treatment was 118 h, and that the maximum time to a normal WBC count was 126 h (Fig. 5). These findings suggest that switching antibiotics rather than increasing the ceftriaxone dose should be considered for patients who do not improve after 5 days of ceftriaxone treatment. In addition, Gram-negative bacteria with AmpC β-lactamase or CTX-M-type β-lactamase were not isolated from any patient in the present study. β-lactam antibiotics exert their

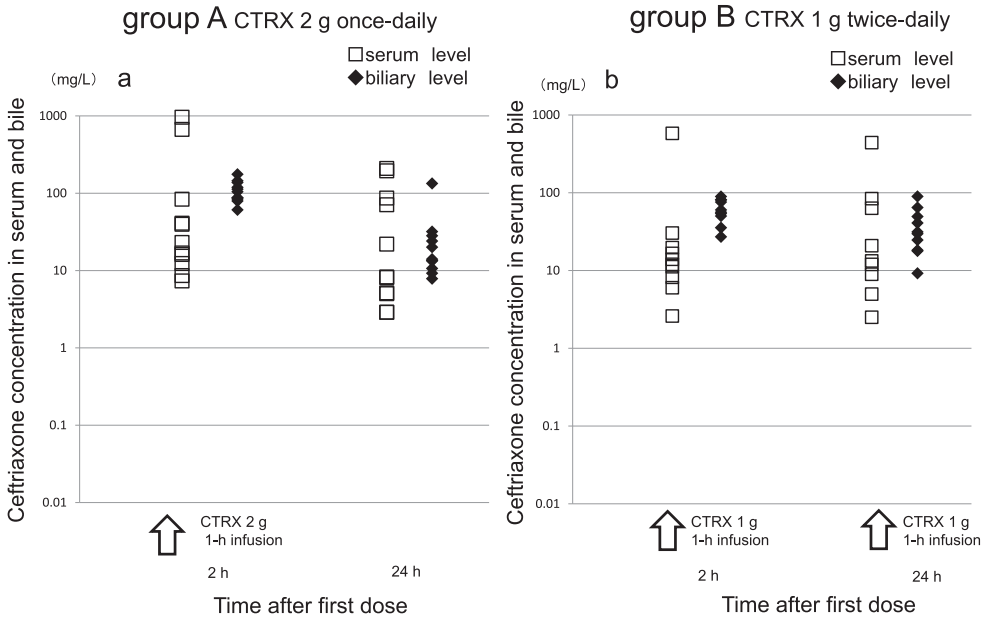

Fig. 3. Comparison of serum and biliary CTRX levels by the number of daily doses a: concentration serum and bile of ceftriaxone in group A, b: concentration of ceftriaxone serum and bile in group B.

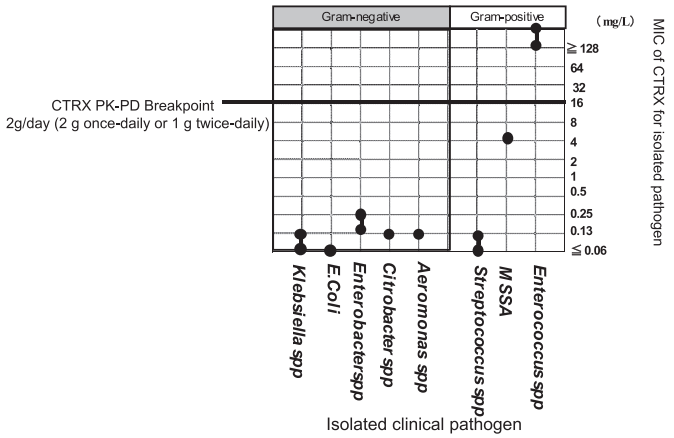

Fig. 4. PK-PD breakpoint of CTRX and MIC of CTRX for isolated pathogen Estimated CTRX PK-PD breakpoint is simulated by 70% of time spent above the MIC. *CTRX*: ceftriaxone.

bactericidal effect in a time-dependent manner, and the %TAM is an important PK–PD parameter for estimating the clinical efficacy of a drug. The target value of this parameter for cephem antibiotics to obtain an anti-proliferative effect and maximum bactericidal effect has been reported to be 40% and 60%–70%, respectively. A PK–PD breakpoint has been set for each dose of each antibiotic so that the %TAM becomes 70%, and the dose and number of doses should be scheduled so that the concentration of each antimicrobial agent is exceed this PK–PD breakpoint. The MIC breakpoint of ceftriaxone is 16 mg/mL for patients receiving 2 g/day (1gx2:1h-div, 2gx1:1h-div) of ceftriaxone [11,19,20]. In the present study, PK–PD breakpoint coverage was 77.8% (7/9 species of isolated clinical pathogens). Thus, our results verified the theoretical efficacy of ceftriaxone against biliary-tract infections determined according to PK–PD breakpoint by comparison with clinical efficacy. PK–PD data are important for determining the dose and frequency of administration of new drugs.

In this study, based on the PK-PD theory, it was confirmed whether differences in the clinical efficacy would occur by dividing the number of doses even if the daily dose of CTRX is the same, but there is no difference in the clinical efficacy. An equivalent clinical efficacy can be expected with either once or twice daily divided doses for moderate to severe AC.

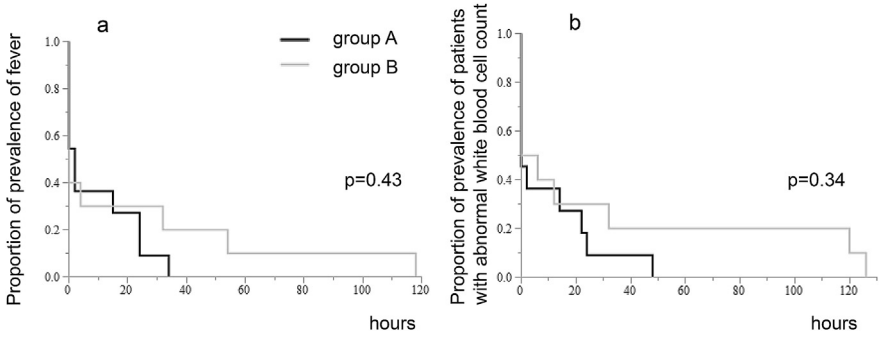

Fig. 5. Time course of clinical efficacy (fever and white blood cell count)a. Proportion of patients with fever is shown by Kaplan-Meiyer curve, b. Proportion of patients with abnormal WBC count is shown by Kaplan-Meiyer curve.

5. Conclusions

We demonstrated that once-daily administration of ceftriaxone (2 g) and twice-daily administration of ceftriaxone (1 g) showed clinical efficacy for moderate-to-severe AC.

Conflicts of interest

None.

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