Efficacy and safety of 3-day versus 7-day cefditoren pivoxil regimens for acute uncomplicated cystitis: multicenter, randomized, open-label trial

Running title: Cefditoren pivoxil for acute uncomplicated cystitis: RCT

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ABSTRACT

Objectives: Fluoroquinolone-insusceptible *Escherichia coli* (*E. coli*) isolated from patients with acute uncomplicated cystitis is a matter of increasing concern. Cefditoren pivoxil (CDTR-PI) is an oral, β-lactamase-stable, extended-spectrum cephalosporin that is effective against fluoroquinolone-insusceptible bacteria. The aim of this study was to evaluate the clinical and microbiological efficacies of CDTR-PI against acute uncomplicated cystitis and to determine the optimal duration of CDTR-PI treatment.

Methods: We compared 3- and 7-day regimens of CDTR-PI administration in a multicenter, randomized, open-label, and study.

Results: A total of 104 female patients with acute uncomplicated cystitis were enrolled and randomized into 3-day (n = 51) or 7-day (n = 53) treatment groups. At first visit, 94 bacterial strains were isolated from the 104 participants of which 81.7 % (85/104) were *E. coli*. Clinical and microbiological efficacies were evaluated 5-9 days following administration of the final dose of CDTR-PI. The clinical efficacies of the 3-day and 7-day groups were 90.9 % (40/44) and 93.2 % (41/44), respectively (P = 1.000). The microbiological efficacies of the 3-day and 7-day groups were 82.5 % (33/40) and

90.2 % (37/41), respectively (P = 0.349). There were no adverse events due to CDTR-PI treatment, with the exception of a mild allergic reaction in one patient, after which the CDTR-PI was exchanged for another antimicrobial.

Conclusions: CDTR-PI is safe and effective for uncomplicated cystitis, with no significant differences in clinical and microbiological efficacies between 3-day and 7-day regimens.

Key words

Cefditoren pivoxil, uncomplicated cystitis, RCTs, optimal duration, *Escherichia coli*

Introduction

Urinary tract infections (UTIs) are the most prevalent bacterial infection in females. The majority of UTIs in otherwise healthy women are acute uncomplicated cystitis, and *Escherichia coli* (*E. coli*) is the most commonly isolated pathogen from UTI patients. According to the guidelines for antimicrobial use published by the Infectious Diseases Society of America and the European Society for Microbiology and Infectious Diseases in 2010, fluoroquinolones and oral cephems are alternative drug,[1] while the first line antimicrobial regimen for the treatment of acute uncomplicated cystitis is a 3-day regimen of fluoroquinolones in the Japanese guidelines published in 2014.[2] However, fluoroquinolone-insusceptible *E. coli* is a matter of increasing concern in Japan. Recently, between 10 % and 30 % of *E. coli* strains isolated from patients with uncomplicated and complicated cystitis were resistant to fluoroquinolones.[3] Therefore, new regimens are needed for treatment of acute uncomplicated cystitis.

Cefditoren pivoxil (CDTR-PI, Brand name: MEIACT, Meiji Seika Pharma Co., Ltd., Tokyo, Japan) is a third-generation oral cephalosporin with good activity against urinary tract pathogens, especially against Gram-negative bacteria. It is stable against

hydrolysis by many common beta-lactamases and is primarily excreted by the kidneys.[4] CDTR-PI has good clinical and antimicrobial efficacies against UTIs, respiratory tract infections and skin infections, which are approved indications in Japan.[5, 6] Therefore, CDTR-PI might be effective in the treatment of antimicrobial resistant UTI-causing pathogens, including fluoroquinolone-insusceptible *E. coli*. The optical duration of CDTR-PI, 3-day or 7-day regimen, for acute uncomplicated cystitis was examined in a randomized study, by evaluating the clinical and microbiological efficacies of CDTR-PI against acute uncomplicated cystitis due to pathogens including fluoroquinolone-insusceptible strains.

Patients and Methods

Study design and population

In this multicentre, randomized, open-label, and study, patients with symptoms of acute uncomplicated cystitis presenting during the previous week were recruited between June 2012 and May 2014 at 12 hospitals or urology clinics in Okayama prefecture.

The inclusion criteria included the following: female aged ≥ 20 year and fever < 37.5°C with any cystitis symptoms, such as micturition pain, urinary frequency, urgency, or lower abdominal pain with pyuria. Pyuria was defined as ≥ 10 white blood cells (WBCs)/μL counted by flow cytometric analysis; ≥ 10 WBCs/mm^3 counted by counting chamber or a positive leucocyte esterase result using urine test paper with uncentrifuged urine; or > 5 WBCs/high power field (hpf) in the sediment of centrifuged urine. Exclusion criteria were the following: occurrence of complicated UTIs, previous UTIs within 4 weeks of the current UTI, treatment with other antimicrobials within the previous 10 days, a previous episode of cephalosporin hypersensitivity, patients who had allergic asthma or hives, immunosuppression, current pregnancy, renal failure or

patients who were judged as ineligible for this study by the investigators because of low compliance. The test antimicrobial was a 100 mg CDTR-PI sodium tablet which was orally administrated three times daily (300 mg/day). Eligible patients were simply assigned to 3- or 7-day treatment groups using an internet registration center (Clinical Research Network: MYTHOS CO., LTD, Osaka, Japan). A dropout was recorded if catheter urine contained < 10^3 CFU (colony-forming unit)/mL of live bacteria or if < 10^4 CFU/mL were detected in midstream urine.

Endpoints

Clinical and microbiological efficacies were evaluated during the second and third visits, respectively. The second visit occurred 5-9 days after the first visit (one day after administration of the final dose), while the third visit took place 7-14 days following completion of CDTR-PI treatment. The endpoints of this study were based on the latest clinical Japanese guidelines for urogenital infections.[2] The primary endpoint was the microbiological outcome 5-9 days after the end of administration; effectiveness was defined as a negative urine culture (< 10^3 CFU/mL). The first of two secondary endpoints was the clinical outcome 5-9 days after the first visit; a clinical cure was

defined as the absence of symptoms. The other secondary endpoint, evaluation of recurrence 4-6 weeks following treatment completion, was evaluated by the return of postcards on which patients wrote whether symptoms had recurred and if they had returned to the same/another clinic for treatment of any recurrence. The Trial protocol is shown in Figure 1.

Antimicrobial susceptibilities

Urine samples were collected at the first visit and 5-9 days following treatment completion (Figure 1). The MICs of clavulanate/amoxicillin (CVA/AMPC), CDTR-PI, faropenem (FRPM), LVX, MIN and FOF were measured using the broth microdilution method in the guidelines published by the CLSI,[7] at the central laboratory (Okayama Medical Laboratory Center, Okayama, Japan). Fluoroquinolone-insusceptible *E. coli* strains were defined as those with a LVX MIC ≥ 4 mg/L. Detection of ESBL-producing *E. coli* strains was performed using the disc diffusion test recommended by CLSI.[8]

Statistical analysis

Continuous data including age were analysed using Student's t-test, and the results were presented as the mean±SD. The discrete data including clinical and microbiological efficacies and recurrence rate were expressed as percentages and compared between 2 groups using the Fisher's exact test by intention-to-treat (ITT) analysis. The data was analyzed using JMP software (ver. 11; SAS, Cary, NC, USA) and $P < 0.05$ was considered to be statistically significant.

Ethics

This clinical study was approved by the Okayama University Institutional Review Board prior to study initiation (Registration no. 1383). The study was registered with the UMIN Clinical Trials Registry (UMIN-CTR), Japan (UMINI000010449) and has been completed. The participants reviewed the informed consent document and received individual counseling with a thorough discussion as to alternative treatment, including nonparticipation.

Results

Study population

A total of 104 female patients were enrolled and randomized into the 3-day treatment group (3-day group; 51 patients) or 7-day treatment group (7-day group; 53 patients). The median age was 47.6 years (range 21-84 years) for the 3-day group and 50.1 years (range 20-84 years) for the 7-day group (P=0.5216). All the urine samples were collected as midstream urine. A total of 94 strains (90.4 %) of bacteria were isolated from urine samples from 104 participants; 10 samples (9.6 %) were negative (Table 1). The largest proportion of strains, 85 of 94 (90.4 %), was *E. coli*, followed by 3 strains (3.2 %) of *Staphylococcus saprophyticus*, 2 strains (2.1 %) of *Klebsiella pneumoniae*, 2 strains (2.1 %) of *Enterococcus faecalis*,1 strain (1.1 %) of *Citrobacter koseri*, and 1 strain (1.1 %) of unidentifiable Gram-negative rods.

Evaluation of microbiological and clinical efficacy

The clinical cure rates of the 3-day and 7-day groups were 90.9 % (40/44) and 93.2 % (41/44), respectively. The microbiological cure rate of the 3-day group was 82.5 %

143 (33/40) and 90.2 % (37/41) for the 7-day group. There were no statistically significant
144 differences in clinical efficacy (P = 1.000; Table 2) or microbiological efficacy (P =
145 0.349; Table 2) between the two groups.

146 **Evaluation of recurrence**

147 Evaluations of recurrence rates 4-6 weeks after treatment completion were 10.2 %
148 (5/49) in the 3-day group and 12.2 % (6/49) in the 7-day group. There was no
149 statistically significant difference between the recurrence rates of the two groups (P =
150 1.000) (Table 2).

151 **Antimicrobial susceptibilities of *E. coli***

152 In total, 85 *E. coli* strains were isolated and 84 were examined for antimicrobial
153 susceptibilities. MIC_{50} and MIC_{90} are shown in Table 3. Ten of 84 strains were
154 fluoroquinolone-insusceptible (11.8 %), but revealed high susceptibility to FRPM and
155 FOF. ESBL-producing *E. coli* strains were detected in 7 of 84 strains (8.2 %), 3 of
156 which (42.9 %) were fluoroquinolone-insusceptible. Microbiological cure rates of
157 patients with fluoroquinolone-insusceptible and/or ESBL-producing *E. coli* strains were

158 90.0 % (9/10) and 85.7 % (6/7), respectively. In cases with an ESBL-producing *E. coli*

159 strain, only 1 patient in the 3-day group had a recurrence (Table 4).

160 **Adverse events**

161 Neither treatment group experienced adverse events due to CDTR-PI therapy, with the

162 exception of one patient who had a mild allergic episode, which was followed by a

163 change to a different antimicrobial.

164

Discussion

We compared 3- and 7-day regimens of CDTR-PI administration in a multicenter, randomized and open-label study. CDTR-PI is safe and effective for the treatment of uncomplicated cystitis, with no significant differences between the two groups in clinical and microbiological efficacies.

Many trials for acute uncomplicated cystitis showed that shorter treatment regimens of FOM, pivmecillinam, fluoroquinolones, SXT or FRPM had the advantages of fewer adverse events, lower costs and better patient compliance.[9-13] Among β-lactams, a 3-day regimen with cefpodoxime proxetile (CPDX-PR) showed efficacy equivalent to that of a 3-day regimen of SXT.[14] Some studies of Japanese patients written in Japanese showed that the microbiological cure rates of 3- or 7-day regimens of cefdinir (CFDN), cefcapene pivoxil (CFPN-PI), and CPDX-PR were 83-98 %.[15-17] In those studies, microbiological efficacies were evaluated during administration; antimicrobials included in urine samples involved microbiological results. In the present study, microbiological cure rates using CDTR-PI were 82.5 % in the 3-day group and 90.2 % in the 7-day group, and microbiological efficacies were evaluated in urine

181 samples 5-9 days following administration of the final dose. The effectiveness of
182 CDTR-PI was determined to be equal to or greater than that of CFDN, CFPN-PI and
183 CPDX-PR.

184 According to the guidelines in Japan, fluoroquionolones have been
185 recommended and the most frequently used for uncomplicated urinary tract infection.
186 Furthermore, also in the USA and Europe, if there are limitations such as availability,
187 allergic history and tolerance, fluoroquinolones and oral cephem should be used.[1] The
188 recent surveillance of antimicrobial susceptibilities of organisms from cystitis patients
189 showed that the proportion of fluoroquinolone-insusceptible strains was > 20 % in
190 Japan.[18] In this study, 80.0 % (8/10) of fluoroquinolone-insusceptible *E. coli* strains
191 were susceptible to CDTR-PI, and CDTR-PI was effective against uncomplicated
192 cystitis caused by fluoroquinolone-insusceptible *E. coli* strains. Furthermore, even in
193 patients with ESBL-producing *E. coli* strains, the microbiological efficacy rate was
194 85.7 % (6/7) and the non-recurrence rate was 83.3 % (5/6). Hatzaki published the paper
195 about antimicrobial susceptibilities of UTI pathogens against cefditoren and reported
196 that all ESBL-producing bacteria were resistant to CDTR-PI.[19] However, Teerapong

and Sadaba reported about pharmacokinetic characteristics of CDTR-PI, that the primary excretion of unchanged drug into the urinary tract was approximately 30 % and that concentrations in urine samples after oral administration of CDTR-PI were very high.[20, 21] Accordingly, concentration of CDTR-PI in urine might be higher than MIC of CDTR-PI against ESBL-producing pathogens. Our data suggest that the use of oral cephems would be an advisable regimen for the initial treatment of acute uncomplicated cystitis, even if the pathogens might be fluoroquinolone-insusceptible and/or ESBL-producing *E. coli*.

With regard to the duration of oral cephems administration for uncomplicated cystitis, some of the studies mentioned above, evaluated while antimicrobials were included in urine samples, recommended 3-day regimens rather than 4-7-day regimens. In our study, with no impact of residual antimicrobials in urine samples, there was no significant difference between 3-day and 7-day groups in clinical and microbiological efficacies. Thus, we suggest that a 3-day treatment regimen of CDTR-PI is one of the first-line therapies for acute uncomplicated cystitis in terms of clinical and microbiological efficacy.

The present study has important limitations. While there was significantly no difference between 2 groups in clinical and microbiological efficacy, larger number of patients might help detecting smaller differences with much power. Also, there were considerable numbers of dropout patients. There were no clear pattern that suggest non-random (systematic) dropout between 2 groups, then we could assume that these dropouts did not essentially affect our results and conclusions. And consistent result for clinical/microbiological outcomes might partly support robustness of our study. Furthermore, one of the reasons that there was no significant difference between 3-day and 7-day groups in clinical and microbiological efficacies might be that Gram-positive cocci including *E. faecalis* or *S. saprophyticus* were rarely detected as a pathogen. Considering not only drop out cases but also pathogens for which efficacy of CDTR-PI might be low, the target number of cases should be set larger. As another limitation, the aim of this study was to compare durations of CDTR-PI administration, not conduct a randomized comparison of fluoroquinolones and cephems. Thus, our data could not strongly recommend cephems rather than fluoroquinolones. Further studies comparing fluoroquinolones, cephems and other antimicrobials, such as FRPM and FOF, and using

229 the latest drug susceptibility data are necessary for the formulation of treatment
230 recommendations for uncomplicated cystitis. As a final limitation, patients had to return
231 a postcard to self-report on disease; therefore, we could not evaluate all patients for the
232 recurrence of cystitis.

Conclusions

The clinical and microbiological efficacy of CDTR-PI therapy for uncomplicated cystitis was assessed in this multicenter, randomized open-label study. The efficacy rates of CDTR-PI were in the same range as found in studies of other oral cephems. Our data suggests that CDTR-PI is one of the potent agents for uncomplicated cystitis and the optimal regimen of CDTR-PI might be 100 mg three times a day for 3 days. Further studies are necessary to evaluate differences in duration or comparisons to other drugs.

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Author contributions

T. S., K. W., A. I., T. W. and H. K. conceived and designed this study and H. K. was the vice president. K. W., A. T., Y. K., M.A., A. I. and T. W. recruited participants and collected specimens. T. S., K. W., T. W. and H. K evaluated the results and facilitated discussions. T. S., K. W., Y. K., M. A. and M. W. performed statistical analyses. M. A., A. I., T. W., Y. N. and H. K. took part in the manuscript writing process and T. S. and K. W. performed overall preparation of the document for submission. All authors approved the final manuscript.

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Figure legends

Figure 1. Trial protocol

Table 1. Causative organisms isolated from urine samples

Table 2. Clinical and microbiological efficacy of CDTR-PI and evaluation of recurrence

399 4-6 weeks after first visit

400 Table 3. Antimicrobial susceptibilities of *E. coli*

401 Table 4. Clinical effects of fluoroquinolone-insusceptible and ESBL-producing *E. coli*