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NOTE

Clinical and microbiological outcomes in treatment of men with non-gonococcal urethritis with a 100-mg twice-daily dose regimen of sitafloxacin

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Abstract Several microorganisms cause non-gonococcal urethritis (NGU). Failure to eradicate *Mycoplasma genitalium* from the urethra could be associated with persistent or recurrent urethritis; thus, the choice of antibiotics with activities potent enough to eradicate *M. genitalium* is crucial in the treatment of NGU. In in vitro studies, sitafloxacin has been shown to be highly active against *Chlamydia trachomatis* and *M. genitalium*. We treated 89 males with NGU, including 15 patients with persistent or recurrent NGU and 1 patient with post-gonococcal urethritis, with a 100-mg twice-daily dose regimen of sitafloxacin to assess its efficacy against NGU. We examined first-void urine samples for the presence of *C. trachomatis*, *M. genitalium*, *Ureaplasma parvum,* and *Ureaplasma urealyticum*. After treatment, we evaluated 73 patients for clinical outcomes and 44 for microbiological outcomes. Symptoms were alleviated in 62 (84.9%) patients, who were judged clinically cured. Microorganisms detected before treatment were eradicated in 42 (95.5%) patients, who were judged microbiologically cured. Regarding microbiological outcomes of specific microorganisms, eradication rates of *C. trachomatis* ($n = 33$), *M. genitalium* ($n = 11$), and *U. urealyticum* ($n = 10$) were 100%, 100%, and 80.0%, respectively. In all 5 patients with *M. genitalium*-positive persistent or recurrent NGU who had experienced treatment failures with antibiotics, the mycoplasma was eradicated. These results suggested that the sitafloxacin regimen used, which was effective on both *M. genitalium* and *C. trachomatis* infections, could be useful as an appropriate option as first- and second-line treatment of NGU.

Keywords Sitafloxacin · Non-gonococcal urethritis · *Chlamydia trachomatis* · *Mycoplasma genitalium* · *Ureaplasma urealyticum*

Urethritis, one of the most common sexually transmitted diseases (STDs) among heterosexual men, is classified as gonococcal or non-gonococcal depending on the presence or absence of *Neisseria gonorrhoeae*. *Chlamydia trachomatis* is a major pathogen of non-gonococcal urethritis (NGU). Recently, *Mycoplasma genitalium*, which was first isolated in urethral cultures from two men with NGU in 1981, has been shown to be another pathogen of male NGU [1]. *Ureaplasma urealyticum* (biovar 2) also has been suggested to be significantly associated with NGU [2]. In addition, some studies have suggested that failure to eradicate *M. genitalium* from the urethra might be responsible for persistent or recurrent NGU [1]. Therefore, when treating men with NGU, it is crucial to choose antibacterial agents that are highly active against not only *C. trachomatis* but also genital mycoplasmas and ureaplasmas. In the current guidelines for treatment of STDs, NGU is not classified into subgroups on the basis of detected pathogens [3]. The guidelines recommend a single-dose regimen of 1 g azithromycin or a 7-day regimen of a twice-daily dose of 100 mg doxycycline for treatment of NGU [3]. They also recommend an erythromycin, levofloxacin, or ofloxacin regimen as alternative treatments. The emergence of drug-resistant *C. trachomatis* has been

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rare, so these regimens have been highly effective in the treatment of chlamydia-positive NGU [4]. For *M. genitalium* infections, however, treatment with the doxycycline regimen has not been so effective [5]. Microbiological eradication of *M. genitalium* with the 1-g dose regimen of azithromycin has been reported to be 72–87% [5, 6]. Additionally, macrolide-resistant clinical strains of *M. genitalium* have been isolated [7]. Although fluoroquinolones are expected to exert bactericidal effect on *M. genitalium*, in vitro tests have shown them to have a wide range of antimicrobial activities against this mycoplasma [8]. Ofloxacin and levofloxacin, which are recommended in the guidelines, are less active than gatifloxacin, moxifloxacin, and sitafloxacin. Clinically, ofloxacin and levofloxacin regimens were found to be not so effective on *M. genitalium*-positive NGU [6, 9, 10], whereas gatifloxacin and moxifloxacin have been shown to be highly effective agents against *M. genitalium*-positive NGU [6, 7, 10, 11]. Sitafloxacin, with its potent activity against *M. genitalium*, is also expected to be a promising agent for NGU, but there are few reports on its efficacy in NGU, including *M. genitalium*-positive NGU. In the present study, we treated 89 men with NGU with a 100-mg twice-daily dose (200-mg total daily dose) regimen of sitafloxacin to assess its efficacy against NGU.

This study was approved by the Institutional Review Board of the Graduate School of Medicine, Gifu University, Gifu, Japan (reference number 20-94). We enrolled 89 Japanese males with NGU who visited a urologic clinic (iClinic) in Sendai, Japan, between April 2009 and July 2011. The subjects ranged in age from 16 to 69 years (median, 30 years), and all were heterosexual. They comprised 73 patients with acute NGU, 15 with persistent or recurrent NGU, and 1 patient with post-gonococcal urethritis (PGU). The patients diagnosed as having acute NGU had not received antibiotic treatment during the 3 months preceding their admission to the clinic. The 15 patients diagnosed as having persistent or recurrent NGU included 4 treated with azithromycin, 4 treated with levofloxacin, 3 treated with doxycycline or minocycline, 1 treated with cefcapene pivoxil, and 3 treated with unknown agents for acute NGU in other clinics. The patient diagnosed as having PGU had been treated for GU with ceftriaxone during the 1 month preceding his enrollment in this study. Every patient provided his informed consent for participation in this study. All had symptoms and signs compatible with NGU, and none showed existence of *N. gonorrhoeae* on examination of their urethral smears.

A first-void urine (FVU) sample, defined as the first 20–30 ml of the initial flush of urine after not having urinated for at least 2 h, was collected from all subjects. A portion of each FVU specimen was examined for quantification of white blood cells (WBCs) with an automated quantitative urine particle analyzer (UF-1000i; Sysmex Corporation, Tokyo, Japan) according to the manufacturer's instruction. All subjects showed 10 or more WBCs per 1 μl FVU. Another portion of each specimen was sent to a laboratory (Mitsubishi Chemical Medience Corporation, Tokyo, Japan) for evaluation of microbial etiology. The urine specimens were tested for *N. gonorrhoeae* and *C. trachomatis* by an APTIMA Combo2 (Gen-Probe, San Diego, CA, USA) assay, and for *M. genitalium*, *Mycoplasma hominis*, *U. parvum,* and *U. urealyticum* by polymerase chain reaction (PCR)-microtiter hybridization assay with species-specific oligonucleotide probes, as reported previously [12]. All subjects were also confirmed to be negative for *N. gonorrhoeae* by the nucleic acid amplification assay.

We treated the patients with sitafloxacin at a dosage of 100 mg twice daily for 7 days. We told them to practice sexual abstinence during treatment and asked them to return for reexamination within 35 days after enrollment, irrespective of the presence or absence of symptoms. Although we also told them that their sex partners should be examined for genital infections, we did not obtain information regarding partner management.

At the successive visits, we examined symptoms and signs of the patients and tested their newly collected FVU samples for microorganisms. We evaluated both clinical and microbiological outcomes. Clinical cure was judged if their symptoms were alleviated. According to the first edition of the Japanese guideline for clinical research of antimicrobial agents on urogenital infections [13], microbiological cure was judged if the microorganism that had been detected in FVU before treatment was eradicated between 22 and 35 days after enrollment.

Of the 89 patients enrolled in this study, 63 were positive for one or more microorganisms of *C. trachomatis*, *M. genitalium*, *M. hominis*, *U. parvum*, and *U. urealyticum*. Between 7 and 34 days after enrollment, 73 patients (82.0%) returned to the clinic and were evaluated for clinical outcomes (Table 1). Symptoms were alleviated in 62 (84.9%) patients, who were judged as clinically cured. The patients who had returned within 21 days after enrollment were excluded from evaluation of microbiological outcomes. Forty-four patients were evaluated for microbiological outcomes, and 42 (95.5%) were judged cured (Table 1). One patient, in whom *U. parvum* that had not been detected at enrollment emerged 28 days after enrollment, was judged microbiologically cured, because this ureaplasma could not be a pathogen of NGU but is a colonizer in the urethra. Two patients were judged to have microbiological treatment failures. In 1 patient, *U. urealyticum* persisted at 26 days after enrollment. In the other patient evaluated 23 days after enrollment, *U. ureaplasma* persisted and *U. parvum* had emerged. Of the 42 patients with microbiological cure, 40 (95.2%) were judged

Table 1 Clinical and microbiological outcomes of patients

At enrollment		At the successive visit				
Organism detected	No. of patients	No. of patients evaluated for clinical outcome		No. of patients evaluated for microbiological outcome[a]		
		Evaluated	Cured	Evaluated	Cured	Failure (persistent and/or replaced organism)
Chlamydia trachomatis	1	1	1	1	1	0
Mycoplasma genitalium						
Ureaplasma urealyticum						
C. trachomatis	4	3	3	3	3[c]	0 (*U. parvum*)
M. genitalium						
C. trachomatis	1	1	1	1	0	1 (*U. urealyticum*)
M. hominis						
U. urealyticum						
C. trachomatis	1	1	1	0	0	0
Ureaplasma parvum						
U. urealyticum						
C. trachomatis	5	3	2	2	1	1 (*U. urealyticum* and *U. parvum*)
U. urealyticum						
C. trachomatis	2 (1)[b]	1 (1)	1 (1)	1 (1)	1 (1)	0
U. parvum						
C. trachomatis	30 (2)	27 (2)	24 (2)	25 (2)	25 (2)	0
M. genitalium	1	1	1	1	1	0
Mycoplasma hominis						
U. urealyticum						
M. genitalium	2 (1)	2 (1)	1 (1)	1	1	0
U. urealyticum						
M. genitalium	1	1	0	0	NA	NA
M. hominis						
M. genitalium	5 (5)	5 (5)	5 (5)	5 (5)	5 (5)	0
U. urealyticum	5 (1)	4	3	4	4	0
M. hominis	1	0	NA	0	NA	NA
U. urealyticum						
U. parvum	4 (1)	2	2	0	NA	NA
None	26 (4)	21 (4)	17 (4)	NA	NA	NA

NA not applicable

[a] According to the first edition of the Japanese guideline for clinical research of antimicrobial agents on urogenital infections [13], microbiological outcomes are evaluated for patients who had returned to the clinic for reexamination between 22 and 35 days after enrollment

[b] Parentheses indicate number of patients with persistent or recurrent non-gonococcal urethritis (NGU)

[c] One patient, in whom *Ureaplasma parvum* that had not been detected at enrollment emerged 28 days after enrollment, was judged microbiologically cured, and is included, because this ureaplasma could not be a pathogen of NGU but a colonizer in the urethra

Table 2 Microbiological outcome of each pathogen

Organism	No. of organisms at the successive visit		Eradication rate (%)
	Evaluated	Eradicated	
Chladymia trachomatis	33	33	100
Mycoplasma genitalium	11	11	100
Ureaplasma urealyticum	10	8	80

clinically cured. Of the 15 patients with persistent or recurrent NGU, 13 were evaluated for clinical outcomes and 8 for microbiological outcomes. All evaluated patients were judged clinically or microbiologically cured.

Microbiological outcomes for pathogens of NGU are shown in Table 2. High eradication rates were observed. In all 11 patients positive for *M. genitalium*, including 5 with persistent or recurrent NGU, the mycoplasma was eradicated.

Because failure to eradicate *M. genitalium* from the urethra could be associated with persistent or recurrent urethritis, it is essential when treating NGU to choose antibiotics with activities potent enough to eradicate both *M. genitalium* and *C. trachomatis* [1]. Among the fluoroquinolone regimens reported previously, the gatifloxacin regimens had higher eradication rates for *M. genitalium* in men with NGU [6, 9–11]. However, this fluoroquinolone is no longer available because of its side effects. In terms of eradication of *M. genitalium*, therefore, the results of the sitafloxacin regimen used in this study suggest that this regimen could be considered as an appropriate option for treatment of NGU. The moxifloxacin regimen has been reported to be highly effective against *M. genitalium* with macrolide resistance selected in patients who experienced NGU treatment failures with azithromycin regimens [6, 7]. In the present study, *M. genitalium* was eradicated in patients with NGU persisting after azithromycin treatment. This sitafloxacin regimen might also be effective against macrolide-resistant *M. genitalium* as a second-line treatment.

In our previous studies, we examined *M. genitalium* DNAs in the urine from patients with NGU for the presence of fluoroquinolone resistance-associated alterations in DNA gyrase and topoisomerase IV and found some alterations in ParC [14, 15]. In Japan, several fluoroquinolones have been developed, and some of them have antimicrobial activity against *C. trachomatis*. Some fluoroquinolone regimens, including ofloxacin and levofloxacin regimens, have been used frequently to treat NGU. These regimens were ineffective against *M. genitalium* infections and might have selected mutants of *M. genitalium* with fluoroquinolone resistance-associated alterations in ParC in clinical practice [6, 9, 10, 14]. In this study, *U. urealyticum* persisted in two of ten patients after treatment. We did not isolate the strains and therefore were unable to determine their susceptibilities to fluoroquinolones, including sitafloxacin. However, the persistence of the ureaplasma might be associated with fluoroquinolone resistance. The emergence and spread of *M. genitalium* and *U. urealyticum* with fluoroquinolone resistance could be a threat to sitafloxacin treatment for NGU. In this study, *M. genitalium* was eradicated by the sitafloxacin treatment in one patient who experienced treatment failure with levofloxacin. To maintain the efficacy of the sitafloxacin regimen, however, care must be taken to select suitable fluoroquinolones and to use sitafloxacin in optimal doses for the treatment of NGU.

Limitations in this study include the small number of subjects, the difficulty in strictly differentiating persistent or recurrent NGU from reinfected NGU, and the lack of analysis of the association of antimicrobial susceptibilities of microorganisms to sitafloxacin with microbiological outcomes. Nevertheless, this study suggested that a 100-mg twice-daily dose regimen of sitafloxacin, which was effective against both *C. trachomatis* and *M. genitalium* infections, could be useful, albeit preliminary, as an appropriate option in the treatment of NGU. In Japan, moxifloxacin is not approved to treat genitourinary tract infections. Therefore, sitafloxacin could be an alternative to moxifloxacin as an antimicrobial agent for a second-line treatment of *M. genitalium* infections unsuccessfully treated with azithromycin regimens.

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