Effect of gatifloxacin against *Mycoplasma genitalium*-related urethritis: an open clinical trial

Ryoichi Hamasuna,[1,2,3] Satoshi Takahashi,[2,4] Hiroshi Kiyota,[2,5] Mitsuru Yasuda,[2,6] Hiroshi Hayami,[2,7] Soichi Arakawa,[2,8] Kazunori Tomono,[9] Tetsuro Matsumoto[1,2]

[1]Department of Urology, School of Medicine, University of Occupational and Environmental Health, Kitakyushu, Japan
[2]Japanese research group for UTI, Japan
[3]Department of Urology, Faculty of Medicine, Miyazaki University, Miyazaki, Japan
[4]Department of Urology, Sapporo Medical University, Sapporo, Japan
[5]Department of Urology, Jikei University Affiliated Aoto Hospital, Tokyo, Japan
[6]Department of Urology, School of Medicine, Gifu University, Gifu, Japan
[7]Blood Purification Center, Kagoshima University Hospital, Kagoshima, Japan
[8]Division of Integrated Medical Education, Department of Social/Community Medical and Health Science, Kobe University Graduate School of Medicine, Kobe, Japan
[9]Infection Control Team, Osaka University Hospital, Osaka, Japan

Correspondence to
Ryoichi Hamasuna, Department of Urology, School of Medicine, University of Occupational and Environmental Health, 1-1 Iseigaoka, Yahatanishi-ku, Kitakyushu, Fukuoka 807-8555, Japan;
hamaryo@med.uoeh-u.ac.jp

Accepted 26 March 2011
Published Online First
28 April 2011

ABSTRACT

Objectives *Mycoplasma genitalium* and *Chlamydia trachomatis* are the primary pathogens detected from non-gonococcal urethritis (NGU). In this study, the efficacy of gatifloxacin was examined against *M genitalium*-related urethritis.

Methods The study was an open clinical trial evaluating the effectiveness of gatifloxacin with 200 mg doses twice a day for 7 days against male NGU.

Results Between March and September 2008, 169 male patients were enrolled, and microbiological and clinical cure rates could be evaluated in 86 patients detected with *C trachomatis* or *M genitalium* and in 135 with NGU, respectively. Microbiological cure rates of gatifloxacin against *C trachomatis* and *M genitalium* were 100% and 83%, respectively, and the total clinical cure rate was 99%.

Conclusion Analysis of in-vivo and in-vitro data from the literature of fluoroquinolone efficacies against *M genitalium* suggests that a MIC90 of 0.125 μg/ml or less may be useful for optimal activity against *M genitalium* infection.

The primary pathogens of non-gonococcal urethritis (NGU) are *Chlamydia trachomatis* and *Mycoplasma genitalium*. The symptoms of chlamydial urethritis and *M genitalium*-related urethritis are quite similar, and patients with NGU have been treated upon their first visit to clinics without knowledge of the specific pathogens underlying their conditions. In any guidelines, either azithromycin or doxycycline regimens are recommended for NGU.[1 2] However, previous studies have demonstrated that doxycycline shows poor efficacy against *M genitalium*-related urethritis,[3] whereas the eradication rates of azithromycin against *M genitalium* were approximately 80%.[4] Fluoroquinolones show good antichlamydial activity, much like tetracycline and macrolides. The ability of moxifloxacin to eradicate azithromycin-resistant *M genitalium* at a lower minimum inhibitory concentration (MIC) has previously been demonstrated,[4–6] but levofloxacin shows a poor activity.[7]

Gatifloxacin is an 8-methoxy fluoroquinolone that shows a broad spectrum and increased antibacterial activities against Gram-positive cocci bacteria, anaerobes, chlamydias and mycoplasmas.[8] The antimicrobial activity of gatifloxacin against *M genitalium* has been shown to be intermediate between those of moxifloxacin and levofloxacin.[6] As gatifloxacin also showed good activities against *C trachomatis*, it could be used as a potential treatment regimen for male NGU; thus, we started an open clinical trial evaluating the effectiveness of gatifloxacin in the treatment of NGU. Unfortunately, gatifloxacin was removed from the US Food and Drug Administration-approved drug list in September 2008 due to serious side effects including abnormal blood glucose levels.[9] The US Food and Drug Administration determination ultimately prevented us from completing this study. Regardless of this, it was decided that this paper would be published because gatifloxacin was an available treatment for NGU at the time it was initiated, and our data provide a potentially useful insight into the treatment of *M genitalium*-related urethritis.

MATERIALS AND METHODS

Patients

Male outpatients more than 20 years old, who had symptoms of urethritis including pus discharge, micturation pain, urethral discomfort and itching, were recruited for this study. Patients gave their written consent and agreed to refrain from sexual activity without condoms between their first and last visits. Patients were excluded from the study if they had diabetes mellitus, displayed an allergy to gatifloxacin, were infected with *Neisseria gonorrhoeae*, were intolerant to gatifloxacin, required therapy with other antimicrobial agents, had severe dysfunction of the heart or liver, were treated with gatifloxacin within the 7 days before the first visit and whose symptoms of urethritis were improving or who had either a history of or diseases relating to epilepsy. The clinicians confirmed the selection and exclusion criteria of the patients for this study and enrolled patients to a specified non-profit corporation, the Supporting Center for Clinical Research and Education, Osaka, Japan, by fax. This study was approved by the ethics committee of Osaka University, Osaka, Japan.

Procedures

Patients with NGU were given a 200 mg dose of gatifloxacin twice a day for 7 days. On the first visit by patients, clinical symptoms were recorded, the first voided urine of patient was analysed and urine specimens for microbiological examination were collected. Patients with less than five white blood cells (WBC) per high power field in the urinary sediments or 10 WBC/μl of uncentrifuged urine specimens were omitted. Patients re-visited the clinic for evaluation 2–3 weeks after gatifloxacin treatment and the same procedures as the first visit were performed. Finally, the efficacy of gatifloxacin was evaluated microbiologically and the clinical cure rates determined at the re-visit.

Urine collection and microbiological examinations are described below. Approximately 20–30 ml

Table 1 Microbiological and clinical outcome of gatifloxacin against NGU

			Microbiological outcomes (n=86)		Clinical outcomes (n=135)			
Urethritis	**Pathogens**	**N**	**CT**	**MG**	**Urethral discharge**	**Micturation pain**	**Urethral discomfort**	**Urethral iching**
CU	CT	68	68/68	–	42/42	33/33	45/46	33/34
	CT+MG	4	4/4	4/4	2/2	3/3	2/2	1/1
NCNGU	MG	14	–	11/14	12/12	9/9	7/7	7/7
	Not detected	48	–	–	33/33	21/21	33/33	23/23
Indeterminate for CT		1	–	–	1/1	–	1/1	1/1
Total		135	72/72	15/18	91/91	66/66	90/91	65/66

CT, *C trachomatis*; CU, chlamydial urethritis; MG, *M genitalium*; NCNGU, non-chlamydial non-gonococcal urethritis; NGU, non-gonococcal urethritis.

of first voided urine was collected from each patient at least 1 h after their latest urination. A total of 2 ml from these specimens was used for the detection of *C trachomatis* and *N gonorrhoeae* using the Aptima Combo2 assay (SRL Co. Ltd., Tokyo, Japan). Then, 8 ml was stored in a freezer until analysis for *M genitalium* and the rest was discarded. Analysis for *M genitalium* was performed at the laboratory of urology, Faculty of Medicine, Miyazaki University, Japan. *M genitalium* was screened by using a real-time PCR assay (TaqMan assay) as described by Jensen *et al*.[10] Specimens with positive results were re-analysed using a 16S ribosomal RNA PCR assay for confirmation.

RESULTS

Between March and September 2008, 169 male patients were enrolled in this study. Among these patients, nine who had had sexual intercourse without a condom during the study period, 22 who did not participate in follow-up visits, two who used other antimicrobial agents and one with an adverse effect (diarrhoea) were omitted. Finally, microbiological and clinical cure rates could be evaluated in 86 patients detected with *C trachomatis* or *M genitalium* and in 135 with NGU, respectively.

In 135 patients with NGU, *C trachomatis* and *M genitalium* were detected from 53% and 13%, respectively (table 1). Microbiological cure rates against *C trachomatis* and *M genitalium* were 100% and 83%. *M genitalium* remained in three patients, but clinical symptoms were cured with or without the eradication of *M genitalium*. Micturition pain and urethral itching remained in two with chlamydial urethritis after the eradication of *C trachomatis*. The total clinical cure rate was 99%.

DISCUSSION

The effectiveness of fluoroquinolones against *M genitalium*-related urethritis is varied. Of the fluoroquinolone compounds tested, the MIC90 values of moxifloxacin, sitafloxacin, gatifloxacin, levofloxacin, ciprofloxacin and norfloxacin were 0.125 μg/ml, 0.125 μg/ml, 0.25 μg/ml, 2 μg/ml, 8 μg/ml and 64 μg/ml, respectively.[6] Of these fluoroquinolones, moxifloxacin, gatifloxacin and levofloxacin were studied clinically, and their microbiological efficacies were 100%,[4] 83% and 25%,[7] respectively. Assuming that fluoroquinolone tissue levels are equivalent for all drugs in this class, an MIC90 of 0.125 μg/ml or less may be necessary for optimal activity against *M genitalium*. These data may be useful in selecting new fluoroquinolones for clinical treatment trials in men with NGU, specifically for the treatment of *M genitalium*. Moxifloxacin is currently not recommended by any of the various sexually transmitted infection treatment guidelines for this purpose and should be studied further in order to be accorded such a recommendation.

In three patients, *M genitalium* was not eradicated. The *M genitalium* DNA loads increased after treatment in only one case (793—275 369 geq). On the last visit, this patient showed no signs of urethral discharge, although the WBC in the urinary sediments remained. In two cases, the *M genitalium* DNA loads decreased (23 373—11 geq, 167020—10 geq), but these specimens were still positive for *M genitalium* by 16S rRNA PCR assay.

Funding This study received funding from the Supporting Center for Clinical Research and Education (SCCRE), Osaka, Japan.

Competing interests None declared.

Patient consent Obtained.

Ethics approval This study was conducted with the approval of the ethics committee of Osaka University, Osaka, Japan.

Contributors RH initiated the study, collected samples and was responsible for analysis of samples for *M genitalium*, participated in data analysis and wrote the first draft of the manuscript. ST, HK, MY, HH and SA participated in planning the study, collected samples and edited the manuscript. KT was a deputy of a specified non-profit corporation, the Supporting Center for Clinical Research and Education, Japan for enrolling patients. TM initiated the study, is a deputy of the study group and edited the manuscript.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. **Workowski KA,** Berman S; Centers for Disease Control and Prevention (CDC). Sexually transmitted diseases treatment guidelines, 2010. *MMWR Recomm Rep* 2010;**59**:1—110.
2. **British Association for Sexual Health and HIV.** Clinical Effectiveness Group: 2007 UK National guideline on the management of non-gonococcal urethritis, Update Dec 2008. http//www.bashh.org/guideline (accessed 21 Apr 2011).
3. **Mena LA,** Mroczkowski TF, Nsuami M, *et al*. A randomized comparison of azithromycin and doxycycline for the treatment of *Mycoplasma genitalium*-positive urethritis in men. *Clin Infect Dis* 2009;**48**:1649—54.
4. **Bradshaw CS,** Jensen JS, Tabrizi SN, *et al*. Azithromycin failure in *Mycoplasma genitalium* urethritis. *Emerg Infect Dis* 2006;**12**:1149—52.
5. **Jensen JS,** Bradshaw CS, Tabrizi SN, *et al*. Azithromycin treatment failure in *Mycoplasma genitalium*-positive patients with nongonococcal urethritis is associated with induced macrolide resistance. *Clin Infect Dis* 2008;**47**:1546—53.
6. **Hamasuna R,** Jensen JS, Osada Y. Antimicrobial susceptibilities of *Mycoplasma genitalium* strains examined by broth dilution and quantitative PCR. *Antimicrob Agents Chemother* 2009;**53**:4938—9.
7. **Maeda S,** Tamaki M, Kubota Y, *et al*. Treatment of men with urethritis negative for *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma parvum* and *Ureaplasma urealyticum*. *Int J Urol* 2007;**14**:422—5.
8. **Fung-Tomc J,** Minassian B, Kolek B, *et al*. In vitro antibacterial spectrum of a new broad-spectrum 8-methoxy fluoroquinolone, gatifloxacin. *J Antimicrob Chemother* 2000;**45**:437—46.
9. **Anon.** Determination that TEQUIN (gatifloxacin) was withdrawn from sale for reasons of safety or effectiveness. *Fed Regit* 2008;**73**:52357—8.
10. **Jensen JS,** Bjornelius E, Dohn B, *et al*. Use of TaqMan 5′ nuclease real-time PCR for quantitative detection of *Mycoplasma genitalium* DNA in males with and without urethritis who were attendees at a sexually transmitted disease clinic. *J Clin Microbiol* 2004;**42**:683—92.