

ORIGINAL ARTICLE

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Clinical efficacy of azithromycin for male nongonococcal urethritis

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Abstract The aim of this study was to confirm the clinical efficacy of a single-dose azithromycin (AZM) regimen (1000 mg) for patients with nongonococcal urethritis in real-life practice. The study finally evaluated 55 patients, 42 who were symptomatic and 13 who were asymptomatic, after excluding 40 who visited clinics only once. Sixteen of the symptomatic patients were diagnosed as having nongonococcal chlamydial urethritis, 7 as having nongonococcal nonchlamydial urethritis, and 19 as having urethritis without any microbial detection. *Chlamydia trachomatis* was detected in 11 asymptomatic patients, *Mycoplasma genitalium* in 1, and *Ureaplasma urealyticum* in 1. Of the patients who were microbiologically evaluated before and after single-dose AZM, microbiological cure was achieved in 87% (20/23) of those with symptomatic nongonococcal urethritis and in 100% (13/13) of those with asymptomatic nongonococcal urethritis. The clinical cure rate was 86% for the 42 symptomatic patients with detectable and undetectable pathogens. There were adverse events in 5 (9%) patients but they were commonly mild and self-limited. In

conclusion, the single-dose AZM regimen was well tolerated and eradicated the estimated and potential pathogens of nongonococcal urethritis.

Key words Azithromycin · Urethritis · *Chlamydia trachomatis*

Introduction

Azithromycin (AZM) is an antimicrobial agent recommended for the treatment of male nongonococcal urethritis (NGU) in the treatment guidelines advocated by the United States Centers for Disease Control and Prevention (CDC)¹ and the Japanese Society for Sexually Transmitted Diseases.² A metaanalysis of randomized clinical trials for the treatment of genital chlamydial infections showed the efficacy of AZM in achieving microbial cure, and its tolerability.³ However, surprisingly few studies have been conducted so far on clinical trials for the treatment of sexually transmitted disease (STD) with AZM in Japan. Therefore, we evaluated the efficacy and tolerability of AZM for male patients with NGU in real-life practice.

Patients and methods

The study was done during the period from September through December 2004. It included male patients with symptomatic NGU who were 20 years old or older. Symptomatic patients with NGU were defined as those having subjective symptoms such as pain on urination or urethral itching, and/or pus discharge from the external urethral meatus. In addition, a white blood cell (WBC) count of 5/high power field (HPF) or more was needed in the microscopic examination of the first voided urine sediments. Asymptomatic patients with NGU were also included in the study if any pathogens were detected. These patients visited us for evaluating genital chlamydial infection because their female sexual partners had been diagnosed as having the

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Table 1. Results for microbiological and clinical cures in the patients with symptomatic urethritis

Urethritis	Detected pathogen	Number	Microbiological cure (%)	Clinical cure (%)
NGCU	<i>Chlamydia trachomatis</i>	13	10/13 (77)	10/13 (77)
	<i>C. trachomatis</i>	2	2/2 (100)	1/2 (50)
	<i>Mycoplasma hominis</i>			
	<i>Ureaplasma parvum</i>			
	<i>C. trachomatis</i>	1	1/1 (100)	1/1 (100)
NGNCU	<i>U. parvum</i>			
	<i>M. genitalium</i>	3	3/3 (100)	3/3 (100)
	<i>U. urealyticum</i>	4	4/4 (100)	3/4 (75)
UWOAMD	–	19	–	18/19 (95)
Total	–	42	20/23 (87)	36/42 (86)

NGCU, nongonococcal chlamydial urethritis; NGNCU, nongonococcal nonchlamydial urethritis; UWOAMD, urethritis without any microbial detection

disease. Patients with a history of allergy for AZM were excluded from the study.

Patients received 1000 mg of AZM orally. No other antimicrobial agents were administered for patients in the study.

Chlamydia trachomatis was detected with Cobas AmpliCor STD-1 *Chlamydia trachomatis/Neisseria gonorrhoeae* (Roche Diagnostics, Brachburg, NJ, USA) by using the first voided urine specimen. *Mycoplasma genitalium*, *Mycoplasma hominis*, *Ureaplasma urealyticum*, and *Ureaplasma parvum* were detected by the polymerase chain reaction (PCR) method reported previously.⁴ These microbiological examinations were performed at Mitsubishi Chemical Medience, Tokyo, Japan.

We evaluated both microbiological cure and clinical cure in the study. Microbiological cure was defined as that occurring when microbiological eradication was achieved at a revisit after the initial treatment, for both symptomatic and asymptomatic patients. Clinical cure was defined as occurring when patients became asymptomatic and the number of WBC decreased to 4 WBC/hpf or less in the first voided urine sediment after treatment, for symptomatic patients. We also assessed adverse reactions due to AZM treatment.

This study was approved by the Institutional Review Board of Sapporo Medical University Hospital and written informed consent was obtained from each patient.

Results

A total of 106 patients participated in the study but 11 patients were excluded because they were microbiologically diagnosed as having gonococcal urethritis (Fig. 1). Of the 95 patients with NGU, 70 were classified as symptomatic and 25 as asymptomatic. Finally, 42 patients with symptomatic NGU and 13 with asymptomatic NGU could be evaluated in the study, as the other patients did not visit the clinic again.

As a result of the microbiological examinations, 16 of the symptomatic patients were diagnosed as having nongonococcal chlamydial urethritis (NGCU), including 2 with *C. trachomatis*, *M. hominis*, and *U. parvum* urethritis and 1

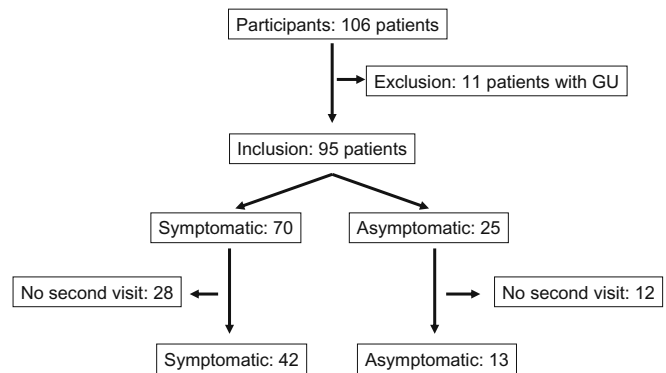


Fig. 1. Flow chart of assessment of patients. GU, Gonococcal urethritis

with *C. trachomatis* and *U. parvum* urethritis (Table 1). Seven of the symptomatic patients had nongonococcal nonchlamydial urethritis (NGNCU) and 19 had urethritis without any microbial detection. Of the patients with NGNCU, *M. genitalium* was detected in 3 and *U. urealyticum* in 4.

Eleven of the asymptomatic patients were diagnosed as having chlamydial urethritis, 1 as having *M. genitalium* urethritis, and 1 as having *U. urealyticum* urethritis.

Microbiological cure was achieved in 87% of the 23 patients with symptomatic NGCU and NGNCU, and in 100% of the 13 patients with asymptomatic NGCU and NGNCU. Clinical cure was obtained in 86% of the 42 patients with symptomatic NGCU, NGNCU, and urethritis without any microbial detection. The microbiological eradication rate for *C. trachomatis* was 89% in 27 asymptomatic and symptomatic patients and, for other organisms, the microbiological eradication rate was 100% in 14 asymptomatic and symptomatic patients. Three patients with NGCU were positive for *C. trachomatis* again at revisit, and 2 of the 3 patients, whose revisits were 1 day and 6 days post-treatment, were still symptomatic. The other patient visited again at 14 days post-treatment. These 3 patients could not be re-examined after the revisits.

There were adverse events in 5 (9%) of the 55 patients (42 symptomatic and 13 asymptomatic) who could be evalu-

ated. Diarrhea was found in 2 patients, gastric pain in 2, and eruption in 1. However, these adverse events were commonly mild and improved soon without any treatment. No patient stopped the AZM treatment because of adverse events.

Discussion

For patients with genital chlamydial infection, the single-dose administration of AZM has already been established as a standard treatment.^{1-3,5} In male patients with genital chlamydial infection, the microbial cure rate with this drug has been reported to be more than 90%.³ In a previous Japanese study,⁶ the eradication rate of *C. trachomatis* was 100% (24 of 24 patients) at 2 weeks post-treatment. In our study, AZM achieved an 89% eradication rate for *C. trachomatis*.

In our study, two of the three patients with NGCU who were positive for *C. trachomatis* again at revisit were positive after treatment probably because they visited again after a very short interval. Thus, nucleic acid would have been detected in nonviable cells, producing a false-positive result. The other patient visited again at 14 days post-treatment. It is possible that the positive result at 14 days was caused by the detection of nonviable cells or by re-infection of the patient. Unfortunately, we could not judge which of these causes was responsible for the positive result, and we were unable to give the three patients additional treatment because they were lost to followup.

The established pathogens for NGU are *C. trachomatis* and *M. genitalium*. *M. genitalium* is an important pathogen for nongonococcal and nonchlamydial urethritis.^{7,8} In the guidelines of the CDC,¹ AZM and doxycycline are recommended for the treatment of patients with NGU. In fact, *M. genitalium* responds better to AZM than to tetracycline.⁹ In addition, the minimum inhibitory concentration of AZM for clinically isolated *M. genitalium* strains is very much lower than those of other antimicrobial agents.¹⁰ In the present study, although the number of isolated *M. genitalium* strains was relatively small, they were eradicated by the single-dose AZM regimen. However, the failure of AZM therapy in *M. genitalium* urethritis has been reported.¹¹ Thus, a more extended course of AZM treatment may be needed for patients with this infection.⁸

Pathogens of male NGU other than *C. trachomatis* and *M. genitalium* have yet to be confirmed clearly. A previous report suggested that *U. urealyticum* was strongly associated with NGU in some patients but *U. parvum* was not.¹² In addition, *U. urealyticum*, *U. parvum*, and *M. hominis* were detected from the urine specimens of asymptomatic healthy male adolescents.¹³ It is possible that these three microorganisms are potential pathogens for NGU; however, the association between these pathogens and NGU is still a matter of debate.

There have been a few reports on the antimicrobial sensitivities of these three microorganisms. In one study,¹⁴ a single-dose AZM regimen eradicated *U. urealyticum* in

78% (7 of 9) patients. In our study, these three microorganisms were eradicated completely by the single-dose AZM regimen. The efficacy of AZM treatment for patients infected by these microorganisms has to be determined because there have been only a few studies including a small number of patients with the disease. Therefore, we need many more studies to determine the significance of these potential pathogens in the development of NGU, and their antimicrobial sensitivities.

For patients with urethritis without any microbial detection, a study in Japan showed that a 7-day treatment with antimicrobial agents active against *C. trachomatis* was also effective.¹⁵ In that study, antimicrobial agents such as minocycline, clarithromycin, levofloxacin, and gatifloxacin were administered to these patients. Our findings suggest that AZM may be an alternative agent for the treatment of urethritis without any microbial detection.

No serious adverse event or discontinuation of AZM occurred in our study. Gastrointestinal adverse events, including diarrhea and gastric discomfort, were common, with the incidence being 7% (4 of 55 patients). Only one patient had eruption. In a previous study with AZM including 236 patients with urethritis in Japan,⁶ 6 patients (2.5%) developed adverse events (4 with diarrhea, 1 with gastric discomfort, and 1 with eruption). A recent study in the United States¹⁴ showed that the most common side effects of AZM were gastrointestinal disorders, with an incidence of 12%. The adverse events were usually mild and self-limited. Clinicians who treat patients with sexually transmitted diseases should note the tolerable but relatively high incidence of gastrointestinal disorders with AZM.

In conclusion, a single-dose AZM regimen was well tolerated and eradicated potential pathogens of NGU. Gastrointestinal side effects were not negligible; however, they were usually mild and self-limited.

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