



Risk Factor Associated with Recurrence after OM-89 (Uro-Vaxom®) Treatment for Female Recurrent Cystitis

Ji-Yeon Han

Department of Urology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, Busan, Korea

Purpose: This study evaluated the risk factors associated with recurrence OM-89 (Uro-Vaxom®) treatment for female recurrent cystitis.

Materials and Methods: The medical records of patients who received OM-89 for at least six months were reviewed retrospectively. Patients were excluded from the analysis if they had an abnormal lower urinary tract anatomy, residual urine volume ≥ 200 ml, a history of genitourinary tuberculosis, urological cancer or pelvic radiation, indwelling urinary catheter, or had genitourinary surgery within the previous six months. Patients were categorized into two groups: (1) no recurrence and (2) recurrent cystitis after OM-89. The risk factors in the two groups were compared. The recurrent cystitis was defined as two more infections in six months or three or more in one year.

Results: A total of 52 female were included. Group 1 had 35 (67.3%) patients and group 2 had 17 (32.7%) patients. Before and after the OM-89, the mean cystitis episodes for six months of groups 1 and 2 were 4.19 ± 4.60 (range, 2-24) and 1.17 ± 1.79 (range, 0-6), respectively, which were decreased significantly ($p < 0.001$). For recurrence after the OM-89, the only risk factor was uncontrolled diabetes (fasting plasma glucose level > 120 mg/dl \pm casual plasma glucose > 180 mg/dl) ($p = 0.002$). No significant differences in the age, menopause, daily water intake, hormone replacement therapy or history of extended-spectrum beta-lactamase-producing *Escherichia coli* were observed between the two groups.

Conclusions: OM-89 was effective in the management of recurrent cystitis in female. On the other hand, uncontrolled diabetes was a risk factor for treatment failure of OM-89.

Keywords: Cystitis; Diabetes mellitus; Immunotherapy; Recurrence

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Correspondence to: Ji-Yeon Han

<https://orcid.org/0000-0002-1695-3100>

Department of Urology, Pusan National University Yangsan Hospital, Pusan National University School of Medicine, 20 Geumo-ro, Mulgeum-eup, Yangsan 50612, Korea

Tel: +82-55-360-2676, Fax: +82-55-360-2164

E-mail: jincomo@gmail.com

INTRODUCTION

Urinary tract infection (UTI) is one of the most common bacterial infections in female. Approximately 40-50% of female have UTI more than once in their lifetime [1]: 27% of the patients with first UTI have a recurrence within the following first six months, and 2.7% experience a second

recurrence in the same period [2]. Recurrent UTI is defined as UTI occurring more than three times during the past 12 months [3]. For some female, recurrent UTI is a cause of serious pain as well as expensive hospital visits, hospitalization, diagnosis, and treatment. Therefore, appropriate preventive measures are needed.

Intermittent or long-term low dose antibiotics is currently

being used as a preventive therapy for recurrent cystitis [4]. On the other hand, antibiotics can lead to resistance of the causative microorganisms. The increasing prevalence of *Escherichia coli* isolates that are resistant to antimicrobial agents has stimulated interest in non-antibiotic methods, such as the oral immunostimulant, OM-89 (Uro-Vaxom®; OM Pharma, Meyrin, Switzerland), for the prevention of recurrent cystitis. In meta-analysis, the risk ratio for the development of at least one UTI was significantly lower in the OM-89 group and the mean number of UTI was approximately half that of the placebo [5,6]. In clinical perspectives, however, the recurrence of cystitis is relatively common after an OM-89 treatment for several months. This study evaluated the risk factors affecting the recurrence of cystitis after OM-89 treatment for female patients with recurrent cystitis.

MATERIALS AND METHODS

The study was approved by the Institutional Review Board of the Pusan National University Yangsan Hospital (IRB no. L-2019-293). The medical records of patients who received OM-89 treatment for recurrent cystitis during at least six months were reviewed retrospectively. Patients who have been experienced at least three episodes of cystitis symptoms (two or more symptoms of dysuria, frequency or burning sensation during voiding) with a urine culture with the isolation of $>10^3$ CFU/ml in at least once in the last year were enrolled in this study. Patients were excluded from the analysis if they had abnormal lower urinary tract anatomy, post-voided residual urine volume ≥ 200 ml, a history of genitourinary tuberculosis, urological cancer or pelvic radiation, indwelling catheter in urinary tract or had genitourinary surgery within the previous six months.

Before the treatment with OM-89, all patients underwent urine culture, urine cytology, and abdomino-pelvic ultrasound, to exclude infection, malignancy, and other pathologies, such as uroflowmetry and post-void residual urine. The presence of diabetes mellitus and a defined fasting plasma glucose level >120 mg/dl \pm casual plasma glucose >180 mg/dl for uncontrolled diabetes was also checked. A 3-day voiding diary was recorded to document the baseline 24-hour urine output. Subsequently, patients received OM-89 as a preventive therapy for recurrent cystitis. The drug was taken once per day before breakfast over a six-month period.

The patients were categorized into two groups: (1) no recurrent cystitis and (2) recurrent cystitis after OM-89 treatment. The risk factors in the two groups were compared. Recurrent cystitis was defined as two more clinical cystitis symptoms with or without the results of the urine culture in six months or three or more in one year.

Statistical analyses were performed using IBM SPSS Statistics 25.0 (IBM Corp., Armonk, NY, USA); a p-value <0.05 was considered significant. Comparative analysis was conducted using a Student's t-test for the continuous variables and Fisher's exact test for the categorical variables.

RESULTS

Table 1 lists the baseline characteristics of the 52 patients enrolled. Before the treatment of OM-89, the mean cystitis episodes for six months of the patients was 4.2.

Before and after the OM-89 treatment for six months, the mean cystitis episodes of the patients over a six month period was 4.19 ± 4.60 (range, 2-24) and 1.17 ± 1.79 (range, 0-6), showing a significant decrease ($p < 0.001$). After the completion of treatment with OM-89, 35 (67.3%) patients had no recurrent cystitis. For the recurrence of cystitis after the OM-89 treatment, the only risk factor was uncontrolled diabetes (fasting plasma glucose level >120 mg/dl \pm casual plasma glucose >180 mg/dl) ($p = 0.002$). No significant differences in age, menopause, daily water intake, hormone

Table 1. Patients' baseline characteristics (n=52)

Variable	Data
Age (y)	54.4 \pm 12.6
Recurrent frequency for 6 months	4.2 \pm 4.6
Menopausal	36 (69.2)
Daily urine output (L)	
< 1	5 (9.6)
1-2	45 (86.5)
> 2	2 (3.8)
Urine culture results	
<i>Escherichia coli</i>	42 (80.8)
ESBL-producing <i>E. coli</i>	5 (9.6)
<i>Enterococcus faecalis</i>	3 (5.8)
<i>Proteus mirabilis</i>	1 (1.9)
<i>Streptococcus agalactiae</i>	1 (1.9)
Diabetes	
No	45 (86.5)
Controlled	2 (3.8)
Uncontrolled	5 (9.6)

Values are presented as mean \pm standard deviation or number (%). ESBL: extended-spectrum beta-lactamase, uncontrolled: fasting plasma glucose level >120 mg/dl \pm casual plasma glucose >180 mg/dl.

Table 2. Clinical characteristics of the patients with recurrent cystitis after OM-89 treatment

Variable	Recurrent cystitis after OM-89 treatment		p-value
	No (n=35)	Yes (n=17)	
Age (y)	52.3±12.4	58.5±12.2	0.105
Frequency of cystitis before treatment in past 6 month	3.7±4.1	5.1±5.5	0.102
Menopausal	23 (65.7)	13 (76.5)	0.435
Hormone replacement therapy	0	1 (5.9)	0.361
Daily urine output (L)			0.801
<1	3 (8.6)	2 (11.8)	
1-2	31 (88.6)	14 (82.4)	
>2	1 (2.9)	1 (5.9)	
ESBL-producing <i>Escherichia coli</i>	4 (11.4)	1 (5.9)	1.000
Diabetes			0.002
No	33 (94.3)	12 (70.6)	
Controlled	2 (5.7)	0	
Uncontrolled	0	5 (29.4)	

Values are presented as mean±standard deviation or number (%). ESBL: extended-spectrum beta-lactamase, uncontrolled: fasting plasma glucose level >120 mg/dl±casual plasma glucose >180 mg/dl.

replacement therapy or history of extended-spectrum beta-lactamase-producing *E. coli* were observed (Table 2).

DISCUSSION

This is the first study to analyze the risk factors associated with the recurrence of cystitis after OM-89 treatment for female patients with recurrent cystitis. Currently, prophylactic antibiotic therapy is considered the most effective method for the treatment of recurrent cystitis. On the other hand, after 6 to 12 months of prophylactic antibiotic treatment, most cases of recurrence will occur if the antibiotic is discontinued [7]. This suggests that antibiotic therapy is not a treatment that meets the fundamental mechanism of infection but is merely an antimicrobial effect by bacterial inhibition around the urethral meatus. In addition, antibiotics can lead to resistance of the causative microorganisms.

The oral immunostimulant OM-89, an extract of 18 serotypes of heat-killed uropathogenic *E. coli*, stimulates the immunity by increasing the number of neutrophils and macrophage phagocytosis and via the up-regulation of dendritic cells [8]. Several clinical studies have also shown that the extracts reduce the incidence of bladder recurrence and the incidence of bacteriuria in patients with recurrent cystitis. A meta-analysis of five clinical trials using OM-89 revealed an average 36% reduction in UTI [6]. Another

meta-analysis of four studies with a total of 891 participants showed that at least one UTI was significantly lower in the OM-89 group (relative risk, 0.61; 95% confidence interval, 0.48-0.78), and mean number of UTI was approximately half compared to the placebo [5]. In a multi-center study in Korea, the incidence of cystitis was reduced significantly from 4.26 for six months to 0.35 for six months after treatment for three months [9]. Nevertheless, the studies did not provide any information on how to optimize treatment. Because only approximately one-third of the UTIs are avoided using this treatment, it would be important to know whether sex, type of infection, hormonal status, or other variables are predictors of the response to the product.

In this study, the only risk factor associated with the recurrence of cystitis after an OM-89 treatment was uncontrolled diabetes (fasting plasma glucose level >120 mg/dl±casual plasma glucose >180 mg/dl) (p=0.002). No significant differences in age, menopause, daily water intake, hormone replacement therapy or history of extended-spectrum beta-lactamase-producing *E. coli* were noted.

Several mechanisms may explain the association between diabetes and UTI. One study reported that urine samples with glucose concentrations between 100 and 1,000 mg/dl (i.e., equivalent to moderate to severe glucosuria) could significantly promote bacterial growth, compared to normal urine [10]. In addition, diabetes increased the adherence of bacteria to uroepithelial cells, particularly *E. coli* expressing type-1 fimbriae [11]. Hyperglycaemia might also alter the immune function in patients with diabetes. This may affect some aspects of the immune reaction, including the polymorphonuclear leukocyte function and adhesion, chemotaxis and phagocytosis [12]. Moreover, this may increase the incidence of UTI in patients with diabetes.

In the present study, the presence of diabetes was not associated with the recurrence of cystitis. Only uncontrolled diabetes affected the recurrence of cystitis after the OM-89 treatment. It was assumed that in the case of unregulated diabetes, the bacterium would become more comprehensible and less effective on the OM-89 for cystitis.

CONCLUSIONS

OM-89 was an effective treatment for the management of recurrent cystitis in female. On the other hand, uncontrolled diabetes was a risk factor for the failure of an

OM-89 treatment. Thorough monitoring and aggressive management of cystitis and the glucose level is needed for patients with recurrent cystitis and unregulated diabetes.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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