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A Long-Term, Multicenter, Double-Blind Study of an *Escherichia Coli* Extract (OM-89) in Female Patients with Recurrent Urinary Tract Infections

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Abstract

Objective: To investigate the long-term preventive effect of the immunotherapeutic OM-89 versus placebo in uncomplicated recurrent UTI in a large cohort of female patients only.

Methods: Adult female patients could enrol in this multicenter, double-blind study if they had acute UTI at the enrolment visit and positive results of urinalysis ($\geq 10^3$ bacteria/ml). Patients received the immunotherapeutic OM-89 or a matching placebo; 1 capsule per day for 90 days, 3 months without treatment, then the first 10 days in Months 7, 8 and 9 and were followed up during 12 months. Primary efficacy criteria were UTI rates over 12 months, distribution of UTIs and proportion of patients with UTI.

Results: A total of 453 patients were treated, 231 in the active group and 222 in the placebo group. Mean rate of post-baseline UTIs was significantly lower in the active group than in the placebo group (0.84 vs. 1.28; $p < 0.003$), corresponding to a 34% reduction of UTIs in patients treated with OM-89. In the active group, 93 patients (40.3%) had 185 post-baseline UTIs, compared to 276 UTIs in 122 patients (55.0%) in the placebo group ($p = 0.001$). The safety profile of OM-89 was good and consistent with that reported in previous studies.

Conclusions: OM-89 significantly reduced the incidence of UTI during the 12 months of the study including 3 months of treatment and three 10-day booster courses. These results confirm that OM-89 is a valuable component of the management of recurrent UTI.

Keywords: Urinary tract infections; Immunotherapy; Bacterial extract; OM-89

1. Introduction

Urinary tract infections (UTI) are commonly encountered in medical practice and range from asymptomatic bacteruria to debilitating acute pyelonephritis (for review see [1,2]). They are especially problematic for women, up to one-third of whom will experience at least one UTI at some point during their lifetime, and are a major cause of morbidity in patients with neuropathic bladder dysfunction and catheterization [3,4]. The predominant pathogen in both complicated and uncomplicated UTI is *E. coli*, although *Klebsiella sp.* and *Proteus* appear with

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increased frequency in complicated UTI, and the empiric use of antibiotics usually brings prompt positive results in the acute phase of infection [2,5].

Recurrent UTI affect women of all ages [2,6]. In a recent epidemiological study performed in the US, 10.8% percent of women aged 18 and older reported at least one presumed UTI during the past 12 months, with the majority of cases occurring among women with a history of two or more previous UTI episodes [7]. These episodes place a large burden on both the patient and healthcare resources; the annual cost of treating UTI in the US alone has been estimated to be $1.6 billion [7].

Low-dose antimicrobial regimens given daily or postcoitally can be effective in preventing recurrences in most women with a predisposition to frequent infection [8], but their use is limited by concerns of bacterial resistance, even for newer generation antibiotics [9,10], and the potential for attenuation of host response [11]. An alternative approach is the oral administration of an immunotherapeutic agent that prevents recurrent UTI without the undesired effects of chronic antibiotic therapy.

OM-89 is a lyophilized extract of selected *E. coli* strains in a capsule formulation containing 6 mg of the bacterial extract. Experimental models have shown that it decreases mortality induced by *E. coli*, *S. typhimurium*, and *P. aeruginosa* [12] in animals, and has activity on macrophages and lymphocytes [13]. Clinical trials performed since 1980 have shown a statistically significant decrease of episodes of UTI in adult, pediatric, pregnant, postmenopausal, or paraplegic patients treated with OM-89 as compared to placebo or to previous reference period [14–21].

The rationale for performing the present study was to investigate further the long-term preventive effect of this agent in uncomplicated recurrent UTI in a large cohort, comprising female patients only.

2. Methods

This was a multinational, double-blind, randomized study of two parallel treatment arms of patients with recurrent UTI enrolled in 52 centers (Austria, Belgium, Czech Republic, Germany, Hungary, Poland, Portugal, Slovak Republic, Switzerland). Ambulatory female patients aged 18–65 years could be included if they had a history of recurrent UTI with at least 3 documented episodes in the previous year, clinical signs of acute UTI persisting at least 2 days, and bacterial count of $\geq 10^3$ in urine. The main exclusion criteria were complicated or neurogenic urogenital disorders, severe fever, severe cardiovascular disease, and renal or hepatic insufficiency. Treatment of acute UTI with antibiotics or antiseptics was allowed. Long-term antibiotic treatment and recent or concomitant immunomodulating therapy were prohibited. The study protocol was approved by ethics committees for all centers, and patients provided written informed consent prior to study entry.

Patients were randomized in blocks of 4 to receive either OM-89 (Uro-Vaxom®; OM PHARMA, Meyrin/Geneva, Switzerland) capsules containing 6 mg of lyophilized lysate of *E. coli* or matching placebo capsules. The randomization list was accessible only to the biometrician during the study, and individual codes could be broken only in case of emergency.

The dosage regimen was one capsule daily during Months 1–3, no treatment in Months 4–6, one capsule daily for the first 10 days each of Months 7–9, and no treatment in Months 10–12.

Six visits were scheduled: enrolment (Day 0), four control visits (Days 30, 90, 180 and 270) and a final visit (Day 360). Additionally, patients were to visit the center as soon as possible in the event of UTI. At the first visit, patients were screened for eligibility according to the inclusion and exclusion criteria. The assessment of the acute UTI included date of onset and the presence of dysuria, burning pain during micturition, and concomitant therapy. Blood and urine samples were taken and a physical examination including vital signs was performed. Patients were instructed on the study conduct, and received test medication as well as diary cards for recording intake of study medication and any signs or symptoms suggestive of UTI. During the control visits, information was collected on adverse events, concomitant medication and intermediary UTI, the diary cards were checked, and study medication and new diary cards were dispensed as appropriate. Treatment compliance was determined by controlling returned blister packs. Urine samples were obtained at the first control visit (Day 30), and blood samples were taken at the third and fifth control visits (Days 90 and 270). Global assessments of efficacy and safety were performed at the sixth and final visit.

Acute UTI was defined as a germ count of $\geq 10^3$/ml in urine [22] occuring after at least one week without anti-infectives and accompanied by at least two of the three symptoms of dysuria, pollakisuria, and burning pain at micturition lasting for a minimum of 2 days.

The primary outcome measures were the rate of acute UTI during 12 months, distribution of UTI per patient, and the proportion of patients with at least one post-baseline UTI. Secondary measures were the intensity of symptoms and duration of acute UTI, the frequency of anti-infective prescriptions and global efficacy assessment by both investigators and patients.

2.1. Statistical methods

All randomized patients with at least one dose of study medication were included in the intention-to-treat (ITT) analysis. The per protocol (PP) population comprised patients who fulfilled all inclusion criteria pertaining to primary diagnosis and treatment, had data from all six visits, were at least 70% compliant with the medication regimen, had no major protocol violations, and were not withdrawn.

Based on an annual rate of 5.5 acute UTI under placebo, $\alpha = 5\%$, $\beta = 20\%$ $(1 - \beta = 80\%)$, two-sided, and an estimated 33% drop-out rate, the sample size was calculated to be 200 patients per treatment group.

The comparison between the two treatment groups was performed by analysis of variance (ANOVA) for the quantitative baseline and demographic data, by Mann–Whitney test for the ordinal data and by χ^2 (or Fisher) test for nominal, categorical or dichotomous data. The comparison of relapse rates between treatment groups was performed using the ANOVA. The proportion of patients with UTI was tested using the Cochran–Mantel–Haenszel test stratified for study site, and distribution of the numbers of UTI per subject was analyzed using the Mann–Whitney test. The

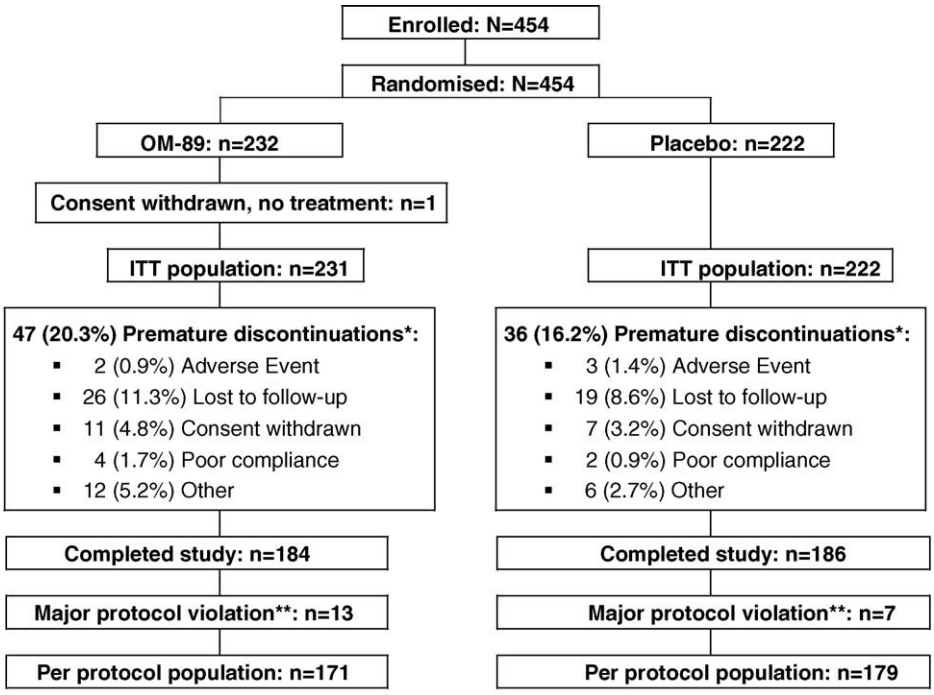

Fig. 1. Patient disposition.

treatment effect was estimated per center and a weighted estimator for the overall treatment effect was calculated according to Fleiss [23]. The 95% confidence intervals were determined for the treatment effect. The secondary efficacy variables were analysed descriptively for exploratory interpretation. The statistical software package SAS (Version 8.0) was used.

3. Results

A total of 454 patients were enrolled, 232 randomized to OM-89 and 222 to placebo. The patient disposition is given in Fig. 1. Treatment arms were comparable for all baseline characteristics except a greater frequency of UTI in the placebo group in the year preceding the study (Table 1). A multiple regression analysis was carried out to adjust for this difference and showed that OM-89 still had a significant effect with respect to placebo on the reduction of UTI recurrences. The most frequently detected pathogen was *E. coli* (Table 2).

In the ITT population, the mean rate of post-baseline UTI, including intermediary visits, was significantly lower in the active group than in the placebo group (0.84 vs. 1.28; $p = 0.0026$, two-sided ANOVA). The unweighted mean treatment effect was −0.44 (95% confidence limits −0.73, −0.15), corresponding to a reduction of 34% of relapse rate in patients treated with OM-89 during the study. The mean rate of UTI was greater in the placebo group than in the active group at all visits, and the overall cumulative group difference was statistically significant in favor of OM-89 ($p < 0.003$, Fig. 2a). The significant treatment effect

Table 1
Patient characteristics by treatment arm (ITT population)

	OM-89 ($n = 231$)	Placebo ($n = 222$)	p-value*
Females, n (%)	231 (100)	222 (100)	N/A
Age (years), mean ± SD	41.7 ± 15.3	39.8 ± 15.1	0.19
Height (cm), mean ± SD**	165.3 ± 6.3	165.6 ± 6.3	0.85
Weight (kg), mean ± SD	64.3 ± 11.7	64.9 ± 13.6	0.89
Number of UTI in previous year, mean ± SD	4.7 ± 2.1	5.2 ± 2.9	0.04

* Two-sided Mann–Whitney tests.
** Not reported for one patient in the OM-89 arm.

Table 2
Type of bacteria at baseline (ITT) [*n* (%)]

	OM-89 ($n = 231$)	Placebo ($n = 222$)
Escherichia coli	162 (70.1)	152 (68.5)
Enterococcus	22 (9.5)	15 (6.8)
Staphylococcus	17 (7.4)	20 (9.0)
Klebsiella	10 (4.3)	10 (4.5)
Streptococcus	9 (3.9)	9 (4.1)
Proteus	5 (2.2)	5 (2.3)

Multiple citations possible.

was confirmed by multiple regression analyses for the number of UTI prior to study, age and center. A comparable result was seen in the per protocol population ($p < 0.001$, Fig. 2b). In the active group, 93 patients (40.3%) had a total of 185 post-baseline UTI, compared to 276 UTI in 122 patients (55.0%) in the placebo group, i.e. a reduction of 14.7% (95% confidence interval –23.8% to −5.6%; two-sided Cochran–Mantel–Haenszel test stratified by center: $p = 0.001$; unadjusted two-sided Fisher's exact test: $p = 0.0019$; estimated odds ratio 0.55). In the first six months of the study, 125 post-baseline UTI were documented in the placebo group compared to 99 in the active group ($\Delta = 26$, −20.1%). Between Month 7 and the end of the study, there were 151 UTIs in the placebo group and 86 UTI in the active group ($\Delta = 65$, −43.0%). As shown in Table 3, the distribution of

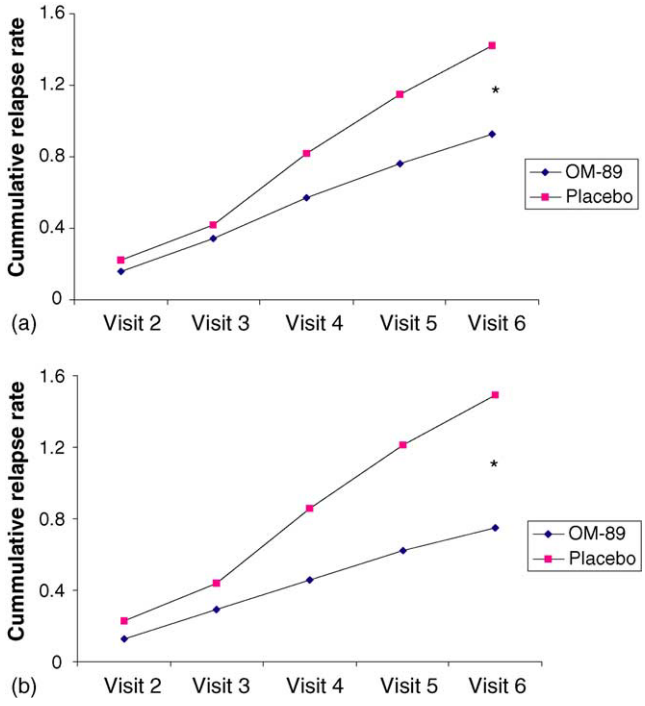

Fig. 2. (a) Cumulative relapse rate of UTI by visit (ITT population; $*p < 0.003$). (b) Cumulative relapse rate of UTI by visit (Per protocol population; $*p < 0.001$).

Table 3
Distribution of post-baseline UTI per patient (p: two-sided Mann–Whitney test)

Number of UTI recurrences	OM-89 ($n = 231$)	Placebo ($n = 222$)
Missing	11 (4.8%)	7 (3.2%)
0	127 (55.0%)	93 (41.9%)
1	46 (19.9%)	53 (23.9%)
2	25 (10.8%)	32 (14.4%)
3	12 (5.2%)	17 (7.7%)
4	3 (1.3%)	7 (3.2%)
≥5	7 (3.0%)	13 (5.9%)
Total number of UTI recurrences	185	276
p	0.0013	

UTI per patient showed a significant group difference in favor of OM-89. Comparable statistically significant results for all primary endpoints were achieved in the supportive per protocol analyses (data not shown).

In the ITT population, the frequency of dysuria, pollakisuria and burning pain decreased more in the active group, without reaching statistical significance (Fig. 3a, b, c). However in the per protocol population, the group difference was significantly in favor of OM-89 for all three symptoms at Visit 4.

The total duration of UTI recurrences (based on the presence of the above symptoms) was reduced by 49% in the OM-89 group with respect to placebo (1.95 ± 3.97 vs. 3.82 ± 8.61 days) with a trend towards statistical significance.

Among patients with bacterial UTI, *E. coli* was the most frequently detected pathogen at each visit, affecting 14–22% of patients across treatment groups and populations compared to 6% or less for all other types of bacteria.

More than 80% of the patients in both treatment groups used anti-infectives at least once during the study. Antibacterial drugs were prescribed for reasons other than UTI in 53.0% of patients in the active group compared to only 40.5% of patients in the placebo group. The mean number of anti-infective prescriptions was 2.44 ± 1.75 in the active group compared to 2.79 ± 2.07 of patients in the placebo group, a significant group difference ($p = 0.005$).

In the global assessment, the majority of patients and investigators in both treatment groups considered that there was a slight or marked improvement, with a rating of "no change" being reported in approximately 10% of patients only.

A total of 161 adverse events (AEs) affected 75 patients in the active group compared to 192 AEs in 71 patients of the placebo group during the course of this clinical trial, with 13% being considered related to treatment in both groups. The most frequent AE was

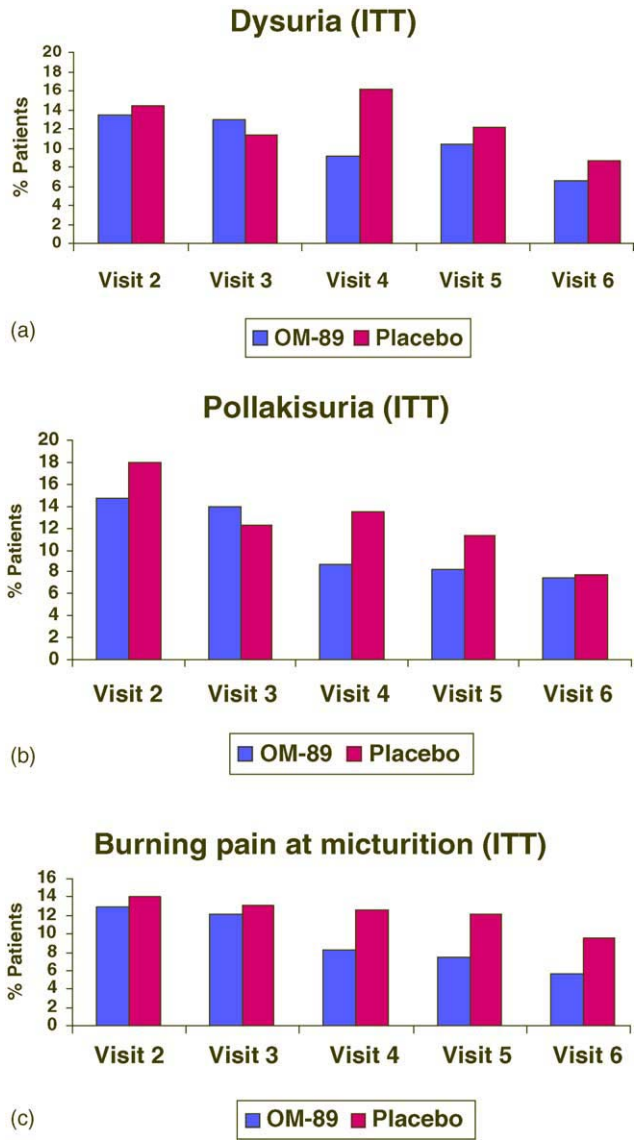

Fig. 3. (a) Frequencies of dysuria over time (ITT). (b) Frequencies of pollakisuria over time (ITT). (c) Frequencies of burning pain at micturition over time (ITT).

headache, followed by gastrointestinal events, amounting to respectively 17 and 15% in both groups. There were 11 serious AEs in the active group and 4 serious AEs in the placebo group, mostly hospitalizations due to sequelae of diseases with onset prior to the study, but none was assessed as related to the study medications by the investigators. There were no safety concerns with regard to laboratory findings, vital signs or physical examinations.

4. Discussion

Recurrent UTI are a common clinical problem, especially among women, and place a large burden on both the patient and healthcare resources [2,6,7]. As the characteristics of UTI vary between males and females due to anatomy and other gender-specific host factors [6], the clinical program of a product aimed at reducing the frequency of UTI needs to include comparative studies in exclusively female cohorts as in the present one.

For all three *a priori* primary efficacy endpoints, the results in both the ITT and PP populations consistently showed significant treatment group differences in favor of the active product. There was a considerably greater reduction of annual relapse rates in both treatment groups in the present study, i.e. from approximately 5 in the year preceding the study to 0.84 for OM-89 and 1.28 for placebo. The results for the placebo group are in contrast to those seen in previous studies, in which the average 6-month relapse rate was 2.5 in patients treated with placebo compared to 1.0 in patients treated with OM-89 [14–21]. This difference can be attributed at least in part to the regular and frequent visits to the clinic over a longer period of time. Nevertheless the results of the present study are consistent with those seen previously, including those of a metaanalysis comprising five randomized studies [24], showing a significant decrease of UTI episodes in patients treated with OM-89 as compared to placebo in both the ITT and PP populations ($p < 0.003$ and $p < 0.001$, respectively).

Symptoms of dysuria, pollakisuria, and burning pain at micturition were less frequent in the active group compared to placebo, although the group difference was statistically significant only at Visit 4 in the per protocol population. These findings corroborate those seen previously. Schulman and coworkers found a significant decrease for dysuria from 96% in both groups at baseline to 11% in the active group compared to 20% in the placebo group after 6 months [17]. In another double-blind, trial, Frey et al. observed a similar effect for dysuria with a significant treatment difference of 24% after 6 months ($p < 0.05$) [14].

The average number of prescriptions for anti-infectives was significantly smaller in the active group ($p = 0.005$). This is in line with the result of a previous randomized study in which antibiotic treatment of UTI was required in 13 out of 86 OM-89-treated patients and in 28 out of 85 placebo-treated patients in a 6-month period ($p = 0.03$, data on file, Pisani et al.).

Until now, the efficacy of OM-89 has been shown for up to 6 months in comparative studies [14–21]. The present study showed persistent treatment effects over the 12-month observation period. Although this study was not designed to quantify the extent to which the

three 10-day booster courses administered in Months 7–9 contributed to the treatment effect, the 43% reduction in the number of UTIs in the active group compared to placebo between Month 7 and the end of the study supports a benefit of these booster courses.

The good safety profile of OM-89 has been determined in clinical studies and by post-marketing surveillance in several countries [14–21]. In the present study, no unexpected treatment-emergent AEs were reported, and no changes in vital signs, physical examinations or laboratory variables were regarded as clinically significant by the investigators.

In conclusion, significant effects of OM-89 on the incidence of UTI were observed during this 12-month study period. From the practitioner's point of view, this therapeutic scheme including three months of treatment and three 10-day booster courses seems to be effective in treating UTI recurrences for a one year period. The good results of the booster courses suggest that they could be repeated in the following year if further recurrences were to occur. Thus the outcomes of this study confirm that OM-89 is a valuable component of the therapeutic management of recurrent UTI. It was well tolerated, and the safety profile seen in this study was consistent with that reported in previous clinical studies.

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Appendix A

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The data management and statistical analysis were performed by B. Plöger and M. Bulitta respectively, CRM GmBh, Rheinbach, Germany.

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Editorial Comment

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For years, the oral administration of immunotherapeutic agents has been considered as an alternative approach to prevent recurrent UTI in women. Particularly Uro-Vaxom®, a bacterial extract of immunostimulating components derived from 18 uropathogenic Escherichia coli strains [1] has demonstrated in vivo increased levels of bacteria-specific serum IgA and IgG, and of total serum IgA, respectively [2]. Furthermore under Uro-Vaxom® an upregulation of PMN activity and an increased activity of macrophages and lymphocytes have been discussed. Already in 1986 an intention-to-treat analysis provided first clinical hints of a positive immunobiotherapeutic effect of the drug [3]. A metaanalysis of further studies demonstrated a positive effect compared with placebo in women with recurrent urinary tract infection for an observation period of 6 months [4].

In the new paper by Bauer and coworkers, a similar preventive effect has been demonstrated for 12 months including 3 months of treatment and 3 short booster courses resulting in a 34% reduction of UTIs under Uro-Vaxom®.

It is well accepted that continuous antimicrobial prophylaxis decreases recurrence of UTI by 95% when compared with placebo [5]. Nevertheless, problems with the compliance have become obvious. Thus, different strategies, e.g. post-coital prophylaxis, self-treatment, cranberry juice intake, have been discussed as alternative prevention strategies [5]. There is no question that safe and effective vaccines would be welcomed as breakthrough. Vaccines, made from combinations of heat-killed uropathogenic strains delivered orally, by injection, or by vaginal suppository are under investigation [6,7]. One promising new approach for the future seems to be the development of a vaccine based on fimbrial components [5,7], questionably hampering bacterial binding to uroepithelial cells.

In my experience, many women with recurrent UTIs are waiting for a ''physiological'', potentially ''immunological'' answer for their recurrent symptoms. The good safety profile of Uro-Vaxom® may help us to discuss this approach with the patients although basic studies to date do not sufficiently elucidate all pathways of the demonstrated beneficial outcome.

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PREVENTION OF RECURRENT URINARY TRACT INFECTIONS IN FEMALE CHILDREN

OM-89 Immunotherapy Compared with Nitrofurantoin Prophylaxis in a Randomized Pilot Study

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ABSTRACT

The aim of this randomized, controlled, open-label pilot study was to compare the efficacy and tolerability of long-term immunotherapy (OM-89) with that of nitrofuran chemotherapy (nitrofurantoin) to prevent recurrent urinary tract infections (UTIs) in female children. Of the 40 patients participating in this study (mean age, 6.5 years; range, 2 to 10 years), 22 were randomly assigned to group A (OM-89) and 18 to group B (nitrofurantoin). The study was carried out in three 6-month phases. In phase I (run-in) both groups were given nitrofurantoin 1 mg/kg/d (a standard prophylactic dose); in phase II, group A received one capsule per day of OM-89 (6 mg/d, active compound), and group B continued the nitrofurantoin treatment. Phase III was a follow-up phase without medication. The diagnosis of a bacterial UTI was based on clinical symptoms (dysuria) and positive urine culture (significant bacteriuria and pyuria). The results show that the oral OM-89 treatment elicits a highly significant decrease in UTIs compared with baseline (6-month prestudy data). The efficacy of the long-term administration of OM-89 in this study was comparable to that of nitrofurantoin during phase II (months 6 to 12) and phase III (months 12 to 18). OM-89 can be considered as an alternative to chemotherapeutic prophylaxis; OM-89 is well tolerated and effective in decreasing the incidence of UTIs in female children prone to recurrences.

INTRODUCTION

Girls, age 6 to 16 years, with bacteriuria are at a greater risk of developing symptomatic urinary tract infection (UTI) than the general population.[1,2] Children with undetected or inadequately treated UTIs are likely to have recurrent infections, chronic pyelonephritis, and, in adulthood, chronic renal failure requiring hemodialysis and renal transplantation.[1,3] A further complication is the continuing emergence of new antibiotic-resistant pathogens, which contributes to the high costs of patient care.[4]

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Leski[5] estimated that 50% of the young women who develop a UTI have a recurrence within 12 months. Etiologically, these reinfections are characterized by a greater adherence of intestinal bacteria to urethral and vaginal epithelia. The increased incidence of such infections also depends on local (within the urinary tract) immunocompetence.

Secretory immunoglobulin A (sIgA) and, to a lesser extent, immunoglobulin M are important mucosal defense mechanisms against colonization by bacteria, viruses, or fungi. It has been reported that levels of sIgA in the urine of female children and adults prone to recurrent UTIs are lower than levels found in uninfected controls,[6,7] thus reducing the mucosal defenses. Stimulating these defenses by elevating the production of sIgA could help reduce the frequency of recurrences. An alternative to antibiotic prophylaxis, which can have a negative effect on the immune system,[8] is the oral administration of immunomodulators. These compounds enhance the patient's own immune defenses against pathogens.

OM-89* is a lyophilized, bacterial proteinic extract obtained from the soluble components of combined alkalinized fractions of the gram-negative bacterium *Escherichia coli,* a pathogen commonly responsible for UTIs. Animal studies have shown that OM-89 prevents experimental infections and stimulates macrophages, phagocytosis, and activity of B lymphocytes and natural killer cells.[9–11] In addition, it increases the level of sIgA and opposes the immunosuppressive effect of certain antibiotics.[11,12] In vitro immunopharmacologic studies have shown that the extract enhances the production of interferon-gamma, tumor necrosis factor-alpha, and other cytokines,[9] as well as the metabolic and functional activities of lymphocytes and macrophages, which are important for host defenses.[10]

This pilot study was designed to compare the efficacy and tolerability of the long-term administration of OM-89 versus nitrofurantoin to prevent reinfection in female children with recurrent UTIs.

PATIENTS AND METHODS

Forty female children with recurrent UTIs participated in this randomized, prospective, controlled study (mean age, 6.5 years; range, 2 to 10 years). Before enrollment, the patients underwent kidney and derivative urinary tract examination using ultrasonography. Children were enrolled in the study if they had had at least three episodes of acute UTIs within the last 12 months. The medical history was well known by the investigators and was documented in the case report form at entry into the study (prestudy data). The diagnosis of bacterial UTI (cystitis, urethritis, cysto-

* Marketed in Germany as Uro-Vaxom® (Sanofi-Winthrop Ltd., Munich) and Uro-Munal® (Deutsche OM Ltd., Friedrichsdorf).

Table I. Criteria used to diagnose urinary tract infections (UTIs).

	Criteria	
	Clinical	**Laboratory**
Acute UTI (cystitis, urethritis, cystourethritis)	Dysuria, urgent, frequent micturition, suprapubic pain; no urinary symptoms in the 4 weeks before the episode	>10 WBCs/mm^3; $>10^{3-5}$ CFU/mL in 1 MSU culture
Acute pyelonephritis	Fever, chills, flank pain; other diagnoses excluded; no history or clinical evidence of urologic abnormalities	>10 WBCs/mm^3; $>10^4$ CFU/mL in 1 MSU culture
Asymptomatic bacteriuria	No urinary symptoms	>10 WBCs/mm^3; $>10^5$ CFU/mL in 2 consecutive MSU cultures >24 hours apart
Recurrent UTI (requiring antimicrobial prophylaxis)	At least 3 episodes of acute infection documented by culture in the last 12 months; no structural or functional abnormalities	>10 WBCs/mm^3; $>10^{3-5}$ CFU/mL in 1 MSU culture

WBC = white blood cells; CFU = colony-forming units; MSU = midstream urine culture.

urethritis) was based on the clinical and laboratory criteria summarized in Table I (adapted from Rubin et al[13]). Patients with obstructive uropathy, chronic pyelonephritis, vesicoureteral reflux, or lithiasis were excluded. Patients with urinary incontinence were given ambulatory bladder training (ie, instructions to drink adequate amounts of liquid and to void frequently and completely at first urge) during the study. The study was approved by the local ethics committee. Parents gave their informed consent before entry.

Patients were randomly assigned to either group A (n = 22) or group B (n = 18). The study consisted of three 6-month phases, with regular control visits at entry and every 3 months thereafter. During phase I all patients were given nitrofurantoin* 1 mg/kg/d in the evening for 6 months. This dosing regimen is the amount required to protect the bladder overnight.

In phase II, group A was switched to OM-89, 6 mg/d lyophilized *E coli* fractions, given as one capsule daily in the morning on an empty stomach. Group B continued treatment with nitrofurantoin during phase II.

Both groups stopped prophylaxis during the final 6-month follow-up period (phase III), as shown in Figure 1. Compliance was assessed at each visit by checking the remaining medication in each patient's box and by questioning the parents.

The diagnosis of a UTI was based on the clinical signs associated with

* Trademark: Furadantin® (Röhm Pharma, Weiterstadt, Germany).

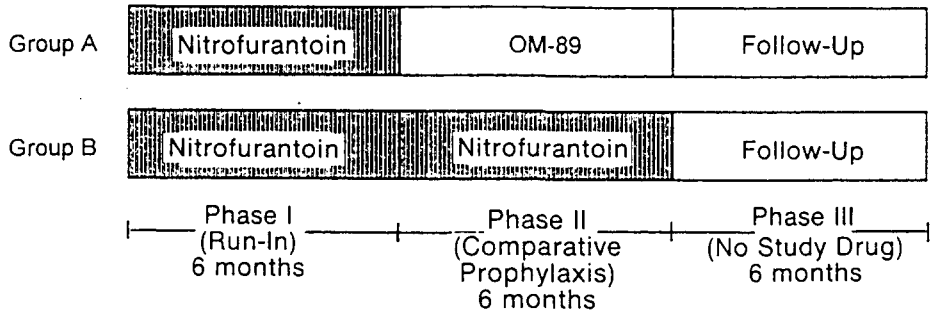

Figure 1. Treatment regimens for patients in group A (n = 22) and group B (n = 18) during the three phases of the 18-month study.

a positive urine culture. Detailed physical examinations, including urine sampling (clean-catch, midstream urine) and urinalysis, were performed at each visit (ie, at entry and after 3, 6, 9, 12, 15, and 18 months) or when acute events occurred. When an acute event occurred, the pathogen was identified microbiologically and its resistance determined to select the appropriate antibiotic treatment.

The efficacy of OM-89 in preventing reinfection was compared with that of standard prophylactic nitrofurantoin therapy used as active-control versus baseline (6-month prestudy data).

At each visit the investigator systematically questioned the patients regarding adverse events. All such events were recorded and subsequently assessed to determine whether they were associated with treatment.

Statistical Analysis

Randomization to the two study groups was determined by the statistical center of the University Hospital, Essen, Germany. All randomized patients were statistically analyzed on an intent-to-treat (ITT) basis for efficacy and tolerability. A per-protocol or best-case approach was used to analyze the ITT patients. Patients with major (pyelonephritis) or minor (missing data) protocol violations were excluded from the per-protocol analysis. Patients with major protocol violations were excluded from the best-case approach; however, patients with only minor protocol violations were not excluded from best-case approach.

The nonparametric Wilcoxon's matched-pairs test was used to assess the frequency of UTIs within groups versus the 6-month prestudy period. The Mann-Whitney-Wilcoxon rank sum test was used for the comparison between groups. (The 95% confidence interval was used for both tests.)

All randomized patients who were correctly allocated, who met the inclusion criteria, and who had at least one control visit at entry were analyzed using the ITT principle. The results are expressed as mean ± SD.

RESULTS

Of the 40 patients who participated in the trial, 22 were randomized to group A (mean age, 6.9 ± 2.8 years) and 18 to group B (mean age, 6.4 ± 2.9 years). These patients constituted the ITT population used to analyze the efficacy and tolerability of the study drugs. Both groups were comparable at entry with regard to age, height, body weight, and frequency of UTIs (Table II). During the study, 1 patient in group A attended the first visit at 3 months (phase I) but did not return for subsequent visits (lack of symptoms, minor protocol violation) (Table III). At the end of phase II, 1 patient receiving OM-89 contracted pyelonephritis (major protocol violation) necessitating antibiotic therapy. In group B, 4 patients did not attend the control visits (3 patients during phase II because they did not have UTI symptoms and 1 during phase III for unknown reasons). A fifth patient in group B developed pyelonephritis during phase III; antibiotic treatment was administered to this patient.

Efficacy

Diagnosis of UTIs was determined on the basis of clinical and laboratory findings. Because 22% of patients (4 of 18) in group B were eliminated from the study during phase III for minor protocol violations (missing data) versus 4.5% of patients (1 of 22) in group A, a best-case approach was used to compensate for this loss. Thus the number and frequency of UTIs in both groups were analyzed using either the per-protocol or best-case approach on an ITT basis. When the per-protocol approach was used, only valid cases (those without major or minor protocol violations) were included. The best-case approach excluded patients with major protocol violations; those with only minor protocol violations were included in the best-case approach. In either case, the number and frequency of UTIs in the patients in group A compared with group B were not significantly different during any phase of the study (Figure 2).

During phase I (the nitrofurantoin run-in phase), one patient in each

Table II. Patient characteristics.

	Group A (n = 22)	Group B (n = 18)
Age (y)	6.9 ± 2.8	6.4 ± 2.9
Height (cm)	123.5 ± 16.4	118.7 ± 18.1
Body weight (kg)	26.6 ± 9.2	22.8 ± 6.9
ESR (mm/h)	0.4 ± 0.5	0.2 ± 0.4
No. of UTIs during the last year	3.8 ± 1.1	3.9 ± 1.0

ESR = erythrocyte sedimentation rate; UTI = urinary tract infection.

Table III. The number of patients available for statistical analysis during the 18-month study and the number of patients excluded and the reasons for exclusion.

	Group A		Group B	
Month	No. of Patients	No. of Exclusions	No. of Patients	No. of Exclusions
Baseline	22	0	18	0
Phase I				
3 Months	21	1 (did not attend control visits)	18	0
6 Months	21	0	18	0
Phase II				
9 Months	21	0	16	2 (did not attend control visits)
12 Months	20	1 (pyelonephritis)	15	1 (did not attend control visits)
Phase III				
15 Months	20	0	14	1 (did not attend control visits)
18 Months	20	0	13	1 (pyelonephritis)

group developed an acute UTI (cystitis). During phase II, 4 patients in group A contracted an acute UTI (3, cystitis; 1, cystourethritis), as did 3 in group B (cystitis). During phase III (follow-up), 3 patients in group A and 4 in group B had an acute UTI of the lower urinary tract (cystitis). In each case, the drug resistance of the pathogen was identified and an antibiotic administered. The bacteria identified during the trial were *E coli, Pseudomonas aeruginosa, Proteus vulgaris, Proteus mirabilis, Enterobacter* species, and *Klebsiella* species.

The overall within-group comparison of the number of UTIs occurring during follow-up versus baseline is shown in Figure 3. In both ITT subpopulations (per-protocol or best-case), the number of UTIs was highly significantly different after treatment compared with baseline (Table IV). The highest significance was observed in group A whether the per-protocol or the best-case approach was used; $P = 0.0001$ (Wilcoxon's matched-pairs test) compared with baseline. Moreover, during phases I and II the differences in both groups compared with baseline were also highly significant (Table IV).

Compliance

Drug compliance was rated as good by the investigator and the patients who attended all the control visits (per-protocol approach: group A, n = 20; group B, n = 13); no additional patients were excluded due to the use of a lower dosage or the interruption of therapy. In group A, attendance at visits was 95.4% (21 of 22), 90.9% (20 of 22), and 90.9% (20 of 22) during phases I to III, respectively. In group B, attendance decreased from 100%

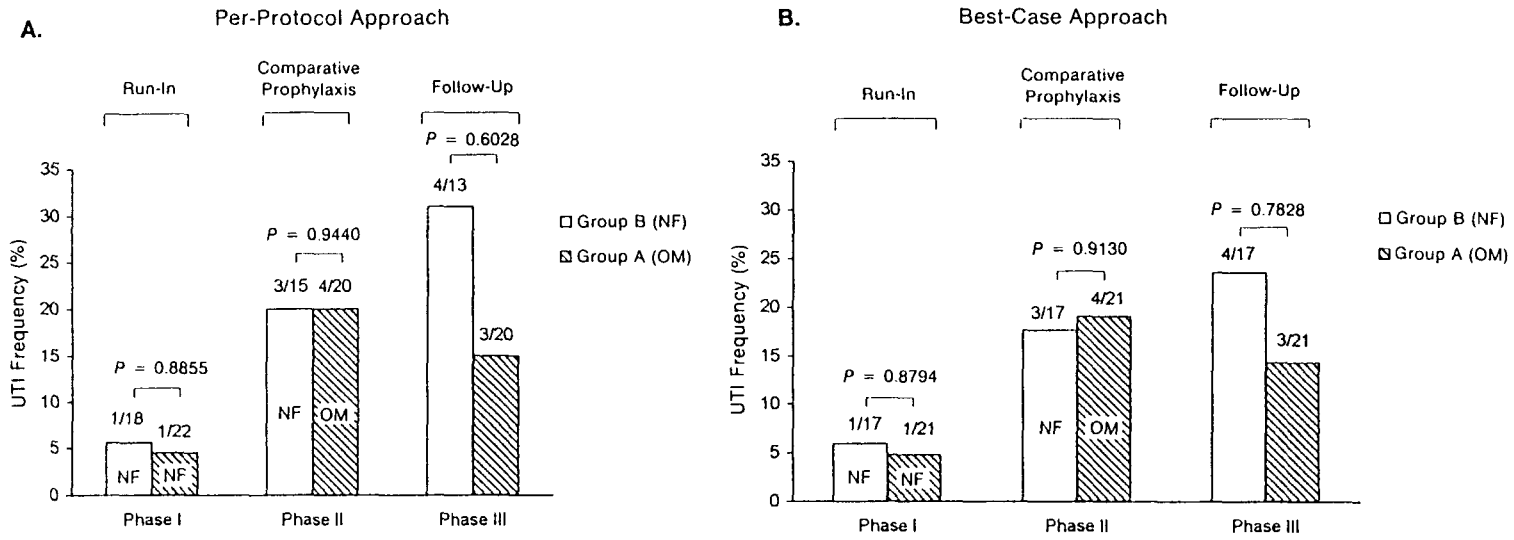

Figure 2. (*A*) Frequency and number of urinary tract infections (UTIs) diagnosed in patients in group A (OM-89) and B (nitrofurantoin) analyzed by a per-protocol approach (considering only valid cases without major and minor protocol violations [ie, pyelonephritis and missing data, respectively]). (*B*) Frequency and number of UTIs diagnosed in groups A and B analyzed by a best-case approach (excluding only major protocol violations [ie, pyelonephritis]). (*P* values between groups determined by the Mann-Whitney-Wilcoxon rank sum test.) NF = nitrofurantoin; OM = OM-89.

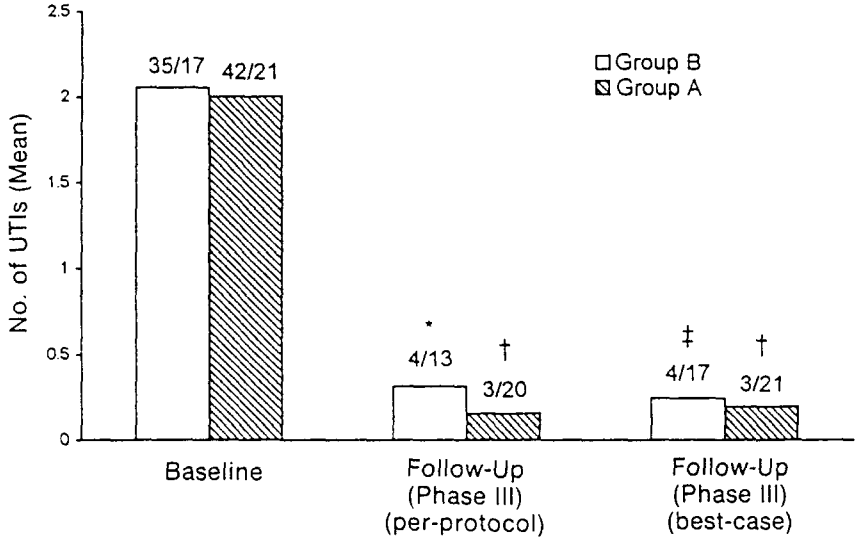

Figure 3. The mean number of urinary tract infections (UTIs) observed during the follow-up versus baseline in group A (OM-89) and group B (nitrofurantoin only), with a per-protocol or best-case approach. (Within-group comparison was analyzed using Wilcoxon's matched-pairs test comparing follow-up with baseline data within groups.) $*P = 0.0015$; $\dagger P = 0.0001$; $\ddagger P = 0.0003$, versus baseline.

(18 of 18) in phase I, to 83.3% (15 of 18) in phase II, and to 72.2% (13 of 18) in phase III. Patients given OM-89 (group A) were rated as having good attendance compliance (pills taken as prescribed); in contrast, patients given nitrofurantoin (group B) had poor attendance compliance (interrupted or discontinued medication).

Tolerability

The tolerability of both long-term treatments was rated as good in the best-case ITT subpopulations (group A: 21 of 22 patients [95.4%]; group B: 17 of 18 patients [94.4%]). Except for patients with pyelonephritis, lack of attendance at control visits was because of the lack of symptoms and not because of side effects. Neither the investigator nor the patients reported any therapy-related adverse events.

DISCUSSION AND CONCLUSIONS

The children admitted to this open-label study were representative of the usual population studied in the management of recurrent UTIs in childhood.[2,14–16] The results show that the oral OM-89 therapy (6 mg/d) was as efficient as nitrofurantoin (1 mg/kg/d) in decreasing the frequency of UTIs during treatment (phase II) and during follow-up (phase III) compared with prestudy data.

Table IV. Urinary tract infections (UTIs) during phases I, II, and III analyzed using the best-case and per-protocol approaches in group A (OM-89) and group B (nitrofurantoin). (Within-group analyses vs baseline [6-month prestudy data] performed with Wilcoxon's matched-pairs test.)

	Phase I (vs Baseline)	Phase II (vs Baseline)	Phase III (vs Baseline)
Best-Case			
Group A			
No. of UTIs	1	4	3
No. of patients	21	21	21
P value	= 0.0001	= 0.0001	= 0.0001
Group B			
No. of UTIs	1	3	4
No. of patients	17	17	17
P value	= 0.0003	= 0.0003	= 0.0003
Per-Protocol			
Group A			
No. of UTIs	1	4	3
No. of patients	22	20	20
P value	= 0.00005	= 0.0001	= 0.0001
Group B			
No. of UTIs	1	3	4
No. of patients	18	15	13
P value	= 0.0002	= 0.0007	= 0.0015

Throughout the study there were no statistically significant differences between the two treatment groups in the frequency of UTIs. During follow-up, a highly significant reduction was observed in both groups in the mean number of UTIs compared with baseline in the best-case ITT population (group A, $P = 0.0001$; group B, $P = 0.0003$). This highly significant decrease in infection rates occurred with both prophylactic regimens. The best-case ITT population analysis, as opposed to the per-protocol approach, was used to correct for the loss of patients in group B (the active control group), knowing that nonattendance at control visits was due to the lack of symptoms of UTI. Thus the best-case approach strengthens the power of the comparison between the patients who received OM-89 and the control patients who received only nitrofurantoin.

The enhanced immunologic defense obtained with OM-89 probably accounts for the long-term decrease in UTIs observed in phase III, as a result of the drug's consolidating effect on the patient's immune status. Another reason for this improvement is the instruction in proper perineal hygiene and ambulatory bladder training (drink adequate amounts of fluid, void frequently and completely, especially before bedtime) that was given to the patients with urinary incontinence.[7]

We found that the tolerability of both drugs was good. Nonattendance at control visits in patients in both treatment groups was not associated with the occurrence of side effects.

Other clinical studies have shown the efficacy of nitrofurantoin in the prevention of recurrences of UTIs.[16,18–20] Studies that used intermittent prophylaxis have shown better compliance and tolerability than studies that used continuous dosing.[21–24] Furthermore, antibiotics and various other chemotherapeutic agents have a spectrum of activity that does not cover numerous resistant organisms. Our observations confirmed the findings of other investigators[25,26] that *Proteus* species and *Pseudomonas* species are resistant to nitrofurantoin. Moreover, the incidence of adverse effects reported with nitrofurantoin is not negligible, whether of gastrointestinal, pulmonary, or neurologic origin[27–30]; although it is generally well tolerated, there has recently been some concern about the slight risk of pulmonary and hepatic fibrosis in children taking nitrofurantoin for prolonged periods.[31] Therefore, another advantage of nonspecific immune stimulation, as with OM-89, is the good tolerability with long-term use.

The results of this study are in accordance with other clinical studies carried out with adults using a double-masked, placebo-controlled design; OM-89 was shown to stimulate the immune defenses and to induce a significant drop in recurrent bacteriuria and dysuria, as well as antibiotic consumption, in patients with recurrent UTIs.[32–34] The activity of OM-89 is elicited by the stimulation of T-cells and of sIgA, the concentration of which was found to be significantly enhanced by OM-89 therapy in female children compared with controls.[35,36]

In conclusion, the stimulation of nonspecific immune defenses with OM-89 is a valuable alternative to and is at least as effective as the low-dose, long-term chemotherapeutic approach commonly used today for prophylaxis of UTIs in female children.

Acknowledgments

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ABSTRACT FORM *Deadline: April 30, 2001*

URO-VAXOM® TREATMENT REDUCED THE NUMBER OF RECIDIVES OF RECURRENT URINARY TRACT INFECTIONS

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Markusovszky Teaching Hospital Szombathely, Hungary

Objective: The aim of the study was to evaluate the efficacy of Uro-Vaxom® treatment among children with recurrent urinary tract infections (UTI).

Patients and methods: 20 children (age 2 –18 year) who had at least 3 UTIs during a one year period were enrolled into the study. Uro-Vaxom® treatment was started after initial laboratory and microbiological investigations. Renal ultrasound and voiding cystogram were also made in all cases. The prophylactic dose of Uro-Vaxom® was 1 capsule/die for 90 consecutive days. The patients were followed up for a one year period. The number of recurrences and the use of antibiotics were registered.

Results: The number of recurrences of the UTIs was 3,64/patient/year before Uro-Vaxom® treatment. The number of recidives was reduced to 1,04/patient/year during and after the Uro-Vaxom® treatment. The difference was strongly significant ($p< 0,001$). The recidive free period was 18,2 weeks/patient/year before treatment vs. 37,66 weeks/patient/year after treatment ($p< 0,001$). Antibiotic therapy was indicated 3,12 times/patient/year before Uro-Vaxom® treatment whereas only 1,04times/patient/year during the study period. Escherichia coli was isolated as the most common pathogen. No side effects were observed during the study period.

Conclusion: Uro-Vaxom® serves as an effective adjuvant therapy for the treatment of recurrent UTI in children. The number of recurrence of UTI is significantly reduced in the Uro-Vaxom® treated group. The administration of Uro-Vaxom® is safe, no side effects were observed during its use.

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A Prospective Multi-center Trial of *Escherichia coli* Extract for the Prophylactic Treatment of Patients with Chronically Recurrent Cystitis

We have assessed the efficacy and safety of *Escherichia coli* extract (ECE; Uro-Vaxom®) which contains active immunostimulating fractions, in the prophylactic treatment of chronically recurrent cystitis. Forty-two patients with more than 2 episodes of cystitis in the proceeding 6 months were treated for 3 months with one capsule daily of ECE and observed for a further 6 months. The primary efficacy criterion was the number of episodes of recurrent cystitis during the 6 months after treatment compared to those during the 6 months before treatment. At the end of the 9-month trial, 34 patients (all women) were eligible for statistical analysis. Their mean age was 56.4 yr (range, 34-75 yr), and they had experienced recurrent urinary tract infections for 7.2±5.2 yr. The number of recurrences was significantly lower during the 6-month follow-up period than during the 6 months preceding the trial (0.35 vs. 4.26, P<0.001). During the follow-up, 28 (82.4%) patients had no recurrences and 4 (11.8%) had 1 each. In patients who relapsed, ECE alleviated cystitis symptoms, including painful voiding, frequency and urgency. There were no serious adverse events related to the study drug. Our study demonstrates the efficacy and safety of ECE in the prophylactic treatment of chronically recurrent cystitis.

Key Words : *Cystitis; Immunization;* Escherichia coli*; OM-8930; Prevention and Control*

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INTRODUCTION

Urinary tract infection (UTI) is a common cause of morbidity and mortality, especially in women, with 25% to 30% of 20 to 40-yr-old women reporting a history of UTI treatment. *Escherichia coli* is by far the most common bacterial pathogen in UTI, accounting for more than 85% of cases of acute cystitis and pyelonephritis as well as for more than 60% of cases of recurrent cystitis (1).

The significant socioeconomic implications of UTI have generated considerable interest in the prevention of recurrences. Although long-term, low-dose antibiotic prophylaxis (e.g. trimethoprim-sulfamethoxazole) has been demonstrated to be highly effective in reducing the risk of recurrent UTI, repeated use of antibiotics has led to bacterial resistance. Other prospects for UTI prophylaxis include natural compounds, bacterial interference and immunization (2). The most commonly used natural compound appears to be cranberry juice. In a double-blind, randomized, controlled study, daily ingestion of 300 mL of cranberry juice reduced bacteriuria with pyuria but failed to decrease the incidence of symptomatic UTIs (3). The concept of bacterial interference is based on not treating asymptomatic colonization, such that "good" bacteria prevent symptomatic UTI caused by "bad" bacteria. There have been provocative data suggesting non-treatment in patient populations with a high prevalence of asymptomatic bacteriuria, including the elderly, school girls and patients with spinal cord injury (4-7), but lack of information on the strains causing asymptomatic colonization in these patient populations is a major limitation of this concept. Immunotherapy may therefore represent the most effective alternative in the prevention of recurrent UTI. For example, oral immunization with *E. coli* extract (ECE; Uro-Vaxom®, OM Laboratories Meyrin/Geneva, Switzerland), a combination of immunoactive fractions of *E. coli* strains, has gained popularity, primarily in European countries. Administration of a lyophilized extract of 18 uropathogens has been found to increase non-specific and specific humoral and cellular immune responses by stimulating the production of interferon-γ and tumor necrosis factor-γ and the activities of lymphocytes and macrophages (8-10).

Although clinical trials of ECE commenced as early as 1980 (11, 12), these studies focused on its efficacy during and for

3 months after treatment, but not for longer periods of time (13, 14). To our knowledge, there have been no clinical studies of ECE in which patients were followed for up to 6 months after treatment. We therefore assessed the efficacy and tolerability of ECE administration in the prophylactic treatment of chronically recurrent cystitis for 6 months after treatment.

MATERIALS AND METHODS

Patients with more than 2 episodes of cystitis, defined as $\geq 10^5$ c.f.u. bacteria/mL and white blood cell (WBC) ≥ 6/HPF in mid-stream urine with concomitant symptoms such as painful and irritating voiding symptoms, during the proceeding 6 months were screened, and 42 patients were enrolled in this multicenter prospective study. Patients with vesicoureteral reflux, obstructive uropathy, urinary lithiasis, renal impairment (defined as serum creatinine >2.5 mg/dL) and urologic procedures that induced UTI were excluded. The study protocol was approved by the institutional review board in each hospital, and all patients provided written informed consent before entry.

At the start of the trial, all patients were in acute recurrence and were therefore treated with antibiotics. After confirming that their urine was sterile, patients were treated for 3 months with one capsule daily of ECE, containing 6 mg of lyophilized immunostimulating fractions, and observed for an additional 6 months without treatment. UTI episodes occurring during the 6 month follow-up period were treated with pertinent antibiotics, and symptom severity was assessed. The degree of urgency was assessed according to the Indevus Urgency Severity Score (IUSS), in which 0 represents no, 1 represents mild, 2 represents moderate, and 3 represents severe urgency. Painful voiding, abdominal/flank pain and fever were each scored according to a similar scale. Frequency was assessed according to a 5 point scale, in which 0 represents >3 hr, 1 <3 hr, 2 <2 hr, 3 <1 hr, and 4 <30 min. Patients who developed UTI during ECE treatment were excluded from the study. Blood chemistry was performed at entry and after 3 months to monitor drug safety. Midstream urine culture and urinalysis were performed at study outset, and 3 and 9 months after the start of ECE treatment, and at any symptom recurrence. At each visit, patients were questioned about compliance and any adverse events.

The primary efficacy criterion was the number of episodes of recurrent cystitis which was measured with the medical record (defined by urinalysis, urine culture, and the presence of concomitant symptoms) during the 6 months after treatment compared to those during the 6 months before treatment. Secondary efficacy criteria included the severity of cystitis symptoms, including dysuria, frequency and urgency, in those who relapsed. Safety evaluations included comparisons of hepatic and renal function and adverse events before and after treatment.

For the determination of sample size, based on an estimated clinical efficacy rate for Uro-vaxom of 80.7% (α=0.05) (15), the sample size was calculated to be 27 patients. Considering an estimated 10% drop-out rate, the actual size of study population should be at least 30 patients. Quantitative data were expressed as mean ± SD. Statistical analyses included parametric one-way ANOVA and nonparametric Wilcoxon's matched-pairs test. Differences were considered significant at $P<0.05$.

RESULTS

Patients

Of the 42 enrolled patients, 8 were excluded, 2 for gastrointestinal problems such as nausea and abdominal pain, 1 for failure to return after the first visit for reasons unrelated to the study medication, 3 for withdrawal of consent, and 2 who developed symptomatic UTI recurrences during ECE treatment. Accordingly, 34 patients were eligible for efficacy analysis at the end of the 9-month trial. All 42 recruited patients were included in the safety analysis. The mean age of the 34 included patients, all women, was 56.4 yr (range 34-75 yr), and they had experienced recurrent UTIs for 7.2 ± 5.2 yr.

Efficacy

The number of recurrences per patient was significantly lower during the 6 months after the end of treatment than during the 6 months prior to treatment (0.35 vs. 4.26, $P<0.001$). During follow-up, 28 patients (82.4%) had no recurrences and 4 (11.8%) had 1 each. In addition, one patient (2.9%) had 2 recurrences and one (2.9%) had 6. Administration of ECE to the 6 patients who relapsed during follow-up alleviated cystitis symptoms, including painful voiding, frequency and urgency (Figs. 1-3). *E. coli* was the organism most frequently isolated from urine, both before (87%) and after (50%) treatment.

We divided the patient population into 2 subgroups: those with 'severe' and 'non-severe' cystitis, defined as ≥ 6 and <6 episodes, respectively, during the 6 months preceding the trial.

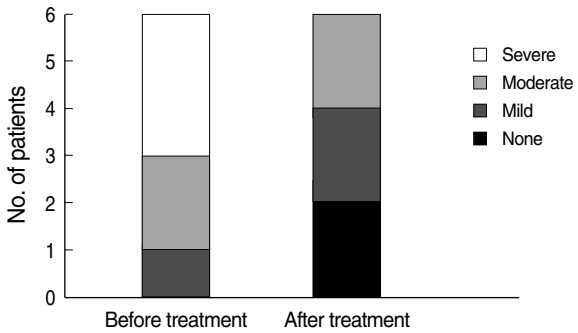

Fig. 1. Changes of urgency in recurred patients (n=6).

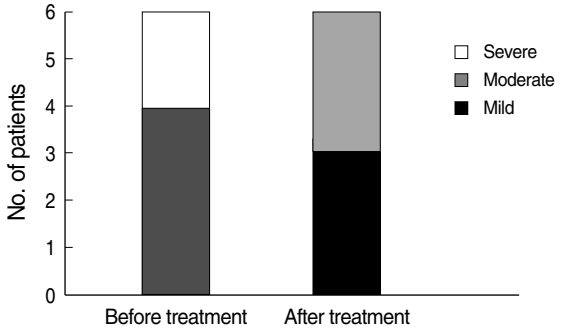

Fig. 2. Changes of painful voiding symptom in recurred patients (n=6).

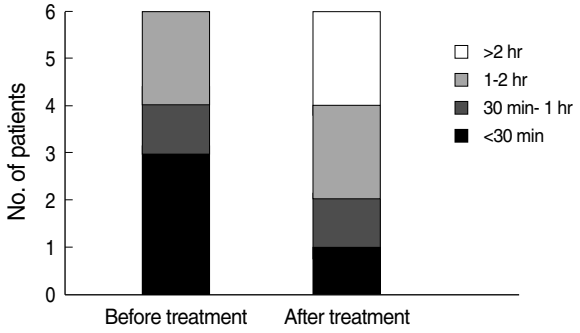

Fig. 3. Changes of frequency in recurred patients (n=6).

Table 1. Results of laboratory studies before and after *E. coli* extract administration

Laboratory studies	Before treatment	After treatment
WBC ($\times 10^3/\mu L$)	6.3±2.1	6.0±1.8
RBC ($\times 10^6/\mu L$)	4.3±0.3	4.3±0.4
Hb (g/dL)	12.5±1.1	12.7±1.1
Hct (%)	38.1±3.2	39±3.1
Plt ($\times 10^6/\mu L$)	256±67	258±61
Neutrophils (%)	56±11.4	53.2±10.3
Lymphocytes (%)	34.3±10.2	37.5±9.1
Monocytes (%)	6.5±2.3	5.5±1.7
Eosinophils (%)	2.6±2.1	2.7±1.8
Basophils (%)	0.6±0.3	0.7±0.4
AST (IU/L)	22.7±5.9	23±6.6
ALT (IU/L)	18.5±7.7	17±7.5
LDH (IU/L)	221.5±78.5	206.5±37
ALP (IU/L)	79.2±50.3	69±30.3
Total bilirubin (mg/dL)	0.7±0.3	0.7±0.2
BUN (mg/dL)	14.1±3.8	13.7±4.5
Creatinine (mg/dL)	0.8±0.1	0.8±0.1

There was no statistically significant differences between two groups ($P>0.05$).
AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; ALP, alkaline phosphatase; BUN, blood urea nitrogen.

Of the 10 patients with 'severe' cystitis, only 3 (30%) experienced recurrences, compared with 3 of 24 patients (12.5%) with 'non-severe' cystitis, a difference that was not statistically significant ($P>0.05$).

Safety

During treatment, 2 patients suffered from mild gastrointestinal problems: one from nausea and the other from abdominal pain, each of which lasted for 1 week. These adverse events ceased when they stopped taking the study drug, and both patients therefore quit the trial. The remaining patients did not complain of any discomfort, including skin pruritus and vertigo, which had been reported in other trials of ECE. Hepatic and renal functions, as assessed in laboratory studies, remained normal after taking ECE (Table 1).

DISCUSSION

The main therapeutic approach in UTI has been the administration of antibiotics, which is usually effective during the acute phase. For patients with chronic or recurrent UTIs, however, repetitive intake of antibiotics, even at clinically therapeutic doses, may lead to the emergence of antibiotic-resistant bacterial strains as well as impairment of the patient's natural immune defense system (16, 17). Although attempts have been made to control or reduce the frequency of acute exacerbations of UTI using natural compounds such as cranberry juice, the results have not been promising (3). In contrast, bacterial vaccines have been shown effective by improving the patient's own immune response (8-10). ECE, an immunomodulating preparation containing the lyophilized extract of 18 uropathogens, has been shown to up-regulate the activity of phagocytes, B-lymphocytes and natural killer cells (8-10, 18). Animal experiments have indicated that repeated oral administration of ECE can stimulate the formation of serum IgA and IgG in mice (19), and to activate bacterial killing by polymorphonuclear cells in rabbits, thus enhancing the clearance of bacteria from the blood stream (20).

ECE has been utilized clinically for more than 20 yr and has a good safety profile. At present, it is used to prevent recurring UTIs in children and adults (11-14, 21, 22). Many clinical trials have assessed the ability of ECE to prevent recurrent UTIs. For example, a double-blind placebo-controlled multicenter study in 166 patients with recurrent UTIs has shown that, during a 3-month observation period, patients on ECE experienced significantly fewer recurrences, less severe signs and symptoms of UTI and decreased usage of antibiotics and chemotherapeutics compared with patients taking placebo (14). In a second trial, in 112 patients with recurrent lower UTIs, patients in the ECE group (n=58) experienced 65.8% fewer episodes of UTIs than patients in the placebo group (n=54), without any critical side effects (13).

Subset analysis showed that only 30% of patients who experienced severe UTI, defined as ≥ 6 cystitis episodes before

the trial, experienced recurrences after treatment, a frequency that did not differ significantly from the 12.5% rate observed in patients with less severe UTI (<6 episodes before treatment). The ability of this *E. coli* extract to prevent recurrences in more recurrent patients indicates that this agent may have greater treatment benefit in patients with more severe UTI.

Although this was not a double-blind, placebo-controlled study, a six-month period before ECE treatment was regarded as internal control to compare to 6 months after ECE treatment. To our knowledge, it is the first clinical trial to investigate the preventive efficacy of ECE for 6 months after the end of treatment. We found that ECE significantly reduced the number of recurrent episodes of UTIs 3.9-fold, as well as the severity of UTI symptoms, including urgency, painful voiding and frequency. These effects of ECE may be due to its enhancement of immune responses, leading to control of bacterial infection.

The mechanism of action of ECE is based on its ability to boost the overall immune system, not on the direct inhibition of *E. coli*. However, we found that ECE treatment reduced the incidence of *E. coli* in urine cultures, although the difference was not significant.

Over the past two decades, ECE has been widely accepted as an effective immunostimulant, with a good safety record. It was reported that most patients treated with ECE experience minor adverse events as frequently as patients in the placebo group. The most frequent adverse events were headache and gastrointestinal side effects, but there were no safety concerns with regard to laboratory variables and clinical signs (23).

Our study also confirmed the safety and efficacy of ECE during and for 6 months after the end of treatment. Repetitive use of antibiotics has been found to suppress the immune system. Patients with frequent UTI recurrences require an immunostimulating drug to prevent further depression of the immune system. The immunostimulant ECE has been shown to effectively suppress the recurrence of cystitis with resultant decrease in severity of UTI symptoms. Our study demonstrates the efficacy and safety of ECE in the prophylactic treatment of chronically recurrent cystitis.

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HIPPOKRATIA 2004, 8, 4: 161-165

ORIGINAL ARTICLE

Immunotherapy with an oral bacterial extract for urinary tract infections

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Background. This study has made to demonstrate efficacy and safety of oral bacterial extracts in reducing the number of urinary tract infection episodes.

Patients and methods. in 20 patients (group A), we gave 1 capsule per day of bacterial extract during 3 months with their conventional antibiotics. All the patients having had more than 2 urinary tract infections during the last 6 months and having actually an acute infection with dysuria, fever and bacteruria. In 10 patients (group B) with the same criteria we did not gave bacterial extract but only antibiotics and we used them as the control group. The duration of the study was 9 months. Women were 60%, chronic renal failure and nephrolithiasis persisted in 20%. Gram(-) bacteria revealed in 80%.

Results. The first 3 months 54% of the patients from group A had none recurrence. After 6 months from the end of receiving bacterial extract in group A:37% had 1 episode and 67% in the control group ($p<0,05$). The intensity and duration of symptoms were diminished in A group in comparison with the control group. Adverse reactions like diarrhoea and headache revealed in 4% not so serious to discontinue the medicine. All the patients finished this protocol.

We conclude that the purified bacterial extracts diminish the intensity and the recurrences of urinary tract infections. They seem to be safe and effective without serious sides effects.

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Lower urinary tract infections are very common infections in the adult population for the nephrologists and urologists. Women represent 80-90% of these patients. 10-20% of the women will have at least one infection episode during their adult life[1,2]. After the initial episode 30% of this population will have at least one recurrence the next 6-12 months. The incidence of recurrences is higher 2 months after the first episode and diminishes thereafter[3,4]. Patients with uncomplicated lower or upper urinary tract infections respond quite well in antibiotics , with full remission in their symptoms. However the overuse of antibiotics has led to the development of resistance. In addition to their relatively high costs and side effects, antibiotics often provide a palliative treatment which is effective against acute infections. In general, antibiotics are powerless to prevent the disease from recurring or from becoming chronic. The recent years patients and doctors have the responsibility to use antibiotics rightly and prudentially[5].

The different serotypes of escherichia-coli are the most common pathogens for lower urinary tract infections , especially responsible for 80-90% of the community infections[6]. In some patients suggest the longterm use of low doses of antibiotics to prevent the infection recurrences. This group include women with more than 2 infection episodes during 6 months, men with chronic prostatitis and asymptomatic pregnant women with bacteruria[7].

As we mentioned the huge use of antibiotics is related with the appearance of resistant bacteria so the alternative strategies are very important. The use of immune-stimulators is a real good option. Ingestion of bacterial products stimulates the responses of different immune cells , resulting in particular in a higher production of secretory IgA at distal mucosal sites[8,9]. Under certain conditions a state of nonreactivity or oral tolerance to ingested bacterial products may occur, probably linked to the formation of suppressor T lympocytes. However, oral immunization generally leads to increased secretory IgA levels in tears, saliva and nasal secretions[9]. Production of secretory IgA also is essential for the prevention of urinary tract infections[10]. Therefore, oral and systemic immunotherapy currently is viewed as a rational approach for the treatment of mucosa-related infections affecting the respiratory, urinary and intestinal tracts[8].

The active principle of the test drug (uro-vaxom, OM Laboratories, Geneva, Switzerland) used consists of standardized immunostimulatory fractions extracted from E.coli strains. These fractions consists essentially of membrane proteins (glycoliproteins) of high molecular weight and of acidic nature (isoelectric point of approximately 4), which is confirmed by the high content in aspartate and glutamate, and the low content in arginine, lysine and histidine. The concentration in endotoxin is less than 0,1μg/mg active principle. The biochemical standarization of the active principle is based on the glycoliprotein content and the efficacy is controlled routinely by the immunological efficacy models(metabolic activation of macrophages and plague –forming cells

test). The extract is administered orally and activates humoral and cell mediated immune responses. Different immunopathological investigations have shown that it confers protection against experimental infections with E. coli and Pseudomonas aeruginosa, and counteracts antibiotic – induced immunosuppression. Furthermore, it stimulates macrophages, B- lymphocytes, natural killer cells and production of secretory immunoglobulins[10,12]. In man the extract increases the synthesis of serum interferon and urinary secretory IgA as well as the number of active T-lymphocytes[12]. Several clinical trials have demonstrated efficient protection against repeated urinary tract infections[13-18]. AIM: the aim of the study was to asses preventive effects of oral bacterial extracts against acute lower and upper urinary tract infections and to evaluate the effect of this agent on the clinical manifestations, frequency, duration and severity of urinary infections and use of conventional therapy.

Patients - Methods

Initially 30 patients suffering from recurrent urinary tract infection were admitted to the trial. The inclusion criteria were: acute urinary infection with at least 10^5 organisms /ml in midstream urine at initial examination on CLED medium (for total organisms) or Mac Concey medium (for gram negative organisms). The patients had at least 2 recurrences of urinary tract infections during the six month preceding the trial. The exclusion criteria were: dysuria without positive bacteriological findings , indwelling catheter, pregnancy and urinary tract abnormalities. Patients who had been treated with corticosteroids, immunosuppressive or immunostimulant agents were excluding too. Patients were divided into two groups. Each patient in the treated group (group A:20 patients), was given one capsule daily in the fasting state, for 3 consecutive months, contained 6 mg of immunostimulating fractions from e.coli in lyophilized form. The treatment period followed by 6 months observation without treatment. Antibiotics and chemotheraputic agents were given as necessary throughout the trial. In group B (10 patients) we gave only antibiotics and we used them as the control group. The study took place over a period of 9 consecutive months during 2002. The 30 patients who were initially chosen for the trial all completed the 6 months period of follow up. The two groups were comparable regarding pretreatment characteristics.

Table 1 summarizes the general characteristics of the two groups. Clinical examination was performed at the beginning and monthly up the 9 months period and at any possible recurrence of infection. A recurrence was defined as the presence of bacteriuria with $> 10^4$ organisms/ml at any examination after the beginning of the trial.

None of the patients admitted to the hospital. The following laboratory data carried out: full blood count, serum concentrations of creatinine, glucose, urea, IgA, IgM, IgG and urine cultures every month. Antibiotics and chemotherapeutics was allowed for the acute infection , was present at entry and for any eventual recurrence. The concomitant antibiotic or chemotherapeutic agent had to be selected between a broad spectrum of penicillin or cotrimoxazole or nitrofuran. Any other antibiotic could be prescribed only if judged necessary. All concomitant illness and drug therapies were recorded. Side effects, detected by direct observation and indirect questioning , were also recorded and their severity , duration and relation to treatment noted. All 30 patients finished this protocol.

Table 1. *The characteristics of the two groups.*

	Group A	Group B
Patients number	20	10
Female	60%	58%
Mean age	52y (19-76y)	55y (24-72y)
CRF	20%	20%
Nephrolithiasis	20%	20%

Statistical analysis

Statistical comparisons were performed by the student t-test, and the level of significance was set up at $p<0,05$.

Results

The symptom of dysuria present in 95% of the patients at the entry of the study, decreased more markendly in the extract group (12% at 3 months and 6 months) than in control group (21% at 3 and 6 months) ($p=0,05$), approaching the limit of statistical significance.

In the urine culture 80% of the patients revealed gram(-) bacteria (ecoli: 82%, proteus: 7%, klebsiella: 1%). Gram(+) in 20% of the patients(staphylococcus: 4%). The mean value of plasma creatinine was: 2,5mg% in group A and 2,1mg% in group B(NS). We had no statistical differences in the mean values of IgA, IgM, IgG in the serum before and after the bacterial extract . Table 2.

The main clinical evaluation criteria, that is the number of urinary recurrences showed a significant better evolution in the extract than in the control group. The number of recurrences with at least 10^5 bacteria/ml was significantly lower in the extract group during the 9 months of the trial.

Three months after the oral administration of bacterial extract 46% of patients in group A and 55% in group B had one recurrence. After 6 months from the end of receiving the bacterial extract, in group A 37% had one episode and 67% in proup B ($p<0,05$). The intensity and duration of symptoms were diminished in A group in relation with the symptoms in the control group.

Table 2. *Changes in the mean values of immunoglobulins.*

immunoglobulin	group	Before treatment	After 3 months	After 6 months
IgG	A	1165.21	1265.55	1400.80
(800-1800mg%)	B(control)	1140.65	1225.35	1200.35
p		ns	ns	ns
IgA	A	199.55	254.55	260.15
(90-450mg%)	B(control)	240.05	247.14	255.15
p		ns	ns	ns
IgM	A	144.53	174.5	175.14
(60-130mg%)	B(control)	145.5	156.5	160.25
p		ns	ns	ns

Table 3. *Recurences 3 months after the oral bacterial extract.*

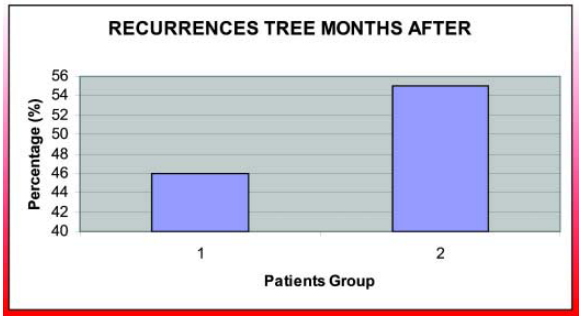
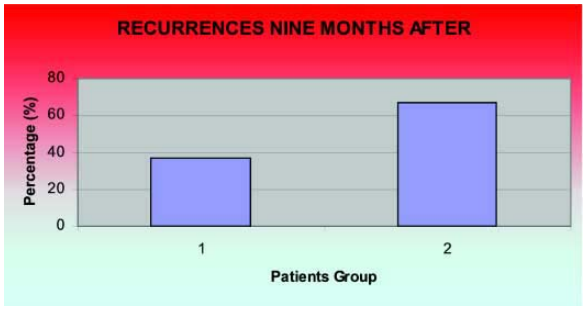


Table 4. *Recurences 6 months after the end of receiving bacterial extracts.*



This decrease in recurrence rate was accompanied by a significant decrease in the consumption of antibiotics and chemotherapeutics (mostly cotrimoxazole and broad spectrum penicillins) which was also more marked during the second half of the study. This antibiotic drug therapy remained the same in 3 and 6 months of observation in the extract group (mean duration 3 days SD:1.1 days) while it increased markedly in the control group. Table 5:

Table 5. *Antibiotic treatment in days*

	extract group	control group	p
initial	5 d (SD:0.5)	5 d (SD:0.8)	NS
3 months	2,7 d (SD:0.9)	3.1 d (SD:1.1)	NS
9 months	3 d (SD:1.1)	9.1 d (SD:2.5)	<0.05

Clinical safety was good, with only 2 side effects reported in the extract group patients. The reported side effects were headache and moderate diarrhoea, no serious enough to discontinue the medicine.

Discussion

The results from this study in 30 patients with acute urinary tract infections have demonstrated the beneficial effect of receiving oral bacterial extracts in management of these infections. The decrease in the number and severity of acute infections in the group with the bacterial extract is in accordance with the results observed by other investigators in series of controlled clinical trials in adults[13-18]. Except the statistically decrease in the number of recurrences in urinary tract infections than placebo does, studies have demonstrated that bacterial extract diminishes the incidence of bacteruria[15,18]. In our study the preventive effect lasted 3 and 6 months after the end of receiving bacterial extract. Shulmann et al 1993 and Popa et al 1996, reported the same effective results[13,14]. However in other clinical trials the beneficial effects of oral administration of these immunostimulants are still relevant 8-12 months after[16,19]. In vitro studies have shown that bacterial extract stimulates the proliferation of lymphocytes[20], stimulates upregulation and downregulation in the metabolic activity of cells[20,21]. Bacterial extract stimulates also the cytokine production , TNF-a [22,23], IL-6[23] and IL-2[22], but we found controversial reports in IL-1 production. It stimulates also the phagocytic activity against S. aureus and candida albicans[23].In vivo trials demonstrated that bacterial extracts stimulate IgG secretion and increase life in infected mice with e-coli, P. aeruginosa[24], it stimulates the production of PFC and anti-SRBC in healthy mice[24] and in immunosupressed mice with antibiotics or mycotoxine[21]. It also stimulates macrophage activity of granulocytes in rabbits[25].

The parameters most frequently chosen to assess efficacy of this medicines are: reduction of the number of infection, reduction in the duration of infection, reduction in the consumption of antibiotics, reduction in absence of work. We focused our observations in the

reduction in the number of infection and in the consumption of antibiotics with quite good results. The duration in antibiotic treatment days diminished significantly especially the second period of our observation except the number of infection recurrences. Effective results in consumption of antibiotics are reported in placebo-control trials to[13,19]. After oral administration, bacterial extract significantly increases the number of T-cells but not the number of B-cells[26]. In the immunoglobulins production we did not notice any significant difference. This may be due to the increased IgA levels in the urinary tract system but not to the systemic blood circulation[11].

Clinical tolerance and safety was good, since reported side effect was minimal with only two side effect reported. In our study this medicine was well tolerated, without serious adverse effects in the examined patients. Other studies refer gastrointestinal disorders and skin reactions but no serious enough to discontinue therapy[26].

In our conclusions patients suffering from recurrent infections in lower and upper urinary tract system may be equipped with a less than normally effective immune response-system. This can be artificially activated by an immunostimulant such this bacterial extract which seems to be safe and effective.

Περίληψη

Μαλλιάρα Μ.* Ανοσοθεραπεία ουρολοιμώξεων με βακτηριακό εκχύλισμα. *Ιπποκράτεια 8 (4):161-165

Σκοπός. Να καταδειχθεί η ασφάλεια και επάρκεια της χρήσης των από του στόματος κεκαθαρμένων βακτηριακών εκχυλισμάτων στην μείωση των υποτροπών των λοιμώξεων του κατώτερου ουροποιητικού.

Ασθενείς και Μέθοδοι. Σε 20 ασθενείς (ομάδα Α) χορηγήσαμε 1 caps βακτηριακού εκχυλίσματος επί 3 συνεχόμενους μήνες με άδειο στομάχι το πρωί ταυτόχρονα με την κατάλληλη αντιβιοτική αγωγή. Όλοι οι ασθενείς είχαν στο ιστορικό τους περισσότερες από 2 ουρολοιμώξεις το τελευταίο εξάμηνο, με συμπτωματολογία δυσουρίας, πυρετού, βακτηριουρίας. Σε άλλους 10 ασθενείς (ομάδα Β) με τα ίδια κριτήρια δεν χορηγήσαμε από του στόματος βακτηριακό εκχύλισμα, αλλά μόνον αντιβιοτική αγωγή και χρησιμοποιήθηκε σαν ομάδα ελέγχου. Η διάρκεια της μελέτης ήταν 9 μήνες. Γυναίκες ήταν σε ποσοστό 60%, χρόνια νεφρική ανεπάρκεια και νεφρολιθίαση εμφάνιζαν σε ποσοστό 20% και στις δύο ομάδες. Λοίμωξη με gram(-) οργανισμούς εμφάνιζαν στο 80%.

Αποτελέσματα. Τρεις μήνες μετά το πέρας της αγωγής με το βακτηριακό εκχύλισμα 54% των ασθενών της ομάδας Α δεν εμφάνισε υποτροπή. 6 μήνες μετά το πέρας της θεραπείας με το βακτηριακό εκχύλισμα 37% των ασθενών της ομάδας Α και 67% της ομάδας Β παρουσίασαν υποτροπή λοίμωξης ($p<0,05$). Η διάρκεια και σοβαρότητα των συμπτωμάτων αναφέρθηκε ελαττωμένη στην ομάδα Α σε σχέση με την ομάδα ελέγχου. Ανεπιθύμητες ενέργειες όπως κεφαλαλγία και διάρροια αναφέρθηκαν σε ποσοστό 4% σε ασθενείς της ομάδας Α, μη ικανές στη σοβαρότητα ώστε να διακοπεί η αγωγή.

Συμπέρασμα. Η χρήση των από του στόματος καθαρμένων βακτηριακών εκχυλισμάτων βοηθά στη μείωση της σοβαρότητας και του αριθμού των υποτροπών σε λοιμώξεις του ουροποιητικού . Τα βακτηριακά εκχυλίσματα φαίνεται πως είναι ασφαλή στην χορήγηση και δεν συνοδεύονται από σοβαρές ανεπιθύμητες ενέργειες.

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