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

Hartwig W. Bauer, Schanaz Alloussi, Günther Egger, Hans-Martin Blümlein, Gabriel Cozma, Claude C. Schulman on behalf of the Multicenter UTI Study Group

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 (≥10³ 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...
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 $\geq10^5$ 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: enrollment (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 $\geq10^3$/ml in urine [22] occurring after at least one week without anti-infectives and accompanied by at least two of the three symptoms of dysuria, pollakiuria, and burning pain during 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 $\chi^2$ (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
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)

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

*Two-sided Mann–Whitney tests.

**Not reported for one patient in the OM-89 arm.
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 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 vs. 3.97 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

### Table 2

<table>
<thead>
<tr>
<th>Type of bacteria at baseline (ITT) [n (%)]</th>
<th>OM-89 (n = 231)</th>
<th>Placebo (n = 222)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em></td>
<td>162 (70.1)</td>
<td>152 (68.5)</td>
</tr>
<tr>
<td><em>Enterococcus</em></td>
<td>22 (9.5)</td>
<td>15 (6.8)</td>
</tr>
<tr>
<td><em>Staphylococcus</em></td>
<td>10 (4.3)</td>
<td>10 (4.5)</td>
</tr>
<tr>
<td><em>Streptococcus</em></td>
<td>9 (3.9)</td>
<td>9 (4.1)</td>
</tr>
<tr>
<td><em>Proteus</em></td>
<td>5 (2.2)</td>
<td>5 (2.3)</td>
</tr>
</tbody>
</table>

Table 3

<table>
<thead>
<tr>
<th>Number of UTI recurrences</th>
<th>OM-89 (n = 231)</th>
<th>Placebo (n = 222)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Missing</td>
<td>11 (4.8%)</td>
<td>7 (3.2%)</td>
</tr>
<tr>
<td>0</td>
<td>127 (55.0%)</td>
<td>93 (41.9%)</td>
</tr>
<tr>
<td>1</td>
<td>46 (19.9%)</td>
<td>53 (23.9%)</td>
</tr>
<tr>
<td>2</td>
<td>25 (10.8%)</td>
<td>32 (14.4%)</td>
</tr>
<tr>
<td>3</td>
<td>12 (5.2%)</td>
<td>17 (7.7%)</td>
</tr>
<tr>
<td>4</td>
<td>3 (1.3%)</td>
<td>7 (3.2%)</td>
</tr>
<tr>
<td>≥5</td>
<td>7 (3.0%)</td>
<td>13 (5.9%)</td>
</tr>
</tbody>
</table>

Total number of UTI recurrences 185 276

$p = 0.0013$
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.

Acknowledgement

The study was supported by a grant from OM PHARMA, Meyrin/Geneva, Switzerland, and there was or is no other financial involvement of any of the authors or members of the Multicenter UTI Study Group.

References


Appendix A

The following investigators were members of the Multicenter UTI Study Group:

**Austria:** Dr W. Kuber, Oberwart; Dr M. Rauchenwald, St Pölten/Niederösterreich; Dr C.P. Schmidbauer, Vienna

**Belgium:** Dr M. van den Bossche, La Louvière; Dr A. Corbusier, Brussels; Dr C. Hauzeur, Montigny-le-Tilleu; Dr M. Naudin, Mons.

**Czech Republic:** Dr L. Horcicka, Prague; Dr M. Reosenberg, Plzen; Dr J. Zmrhal, Melnik.

**Germany:** Dr D. Berger, Cologne; Dr H. Berger, Köln; Dr A. Brickenkamp, Krefeld; Dr F. Degenhardt, Ingolstadt; Prof Z. Fahmy, Bad Kreuznach; Dr J. Gleissner, Wuppertal; Dr S. Görg, Mörfelden-Waldorf; Dr P. Gratzeke, Rosenberg; Dr K. Hess, Hannover; Dr M. W. Kabbani, Bad Camberg; Dr H. Karstedt, Gelsenkirchen; Dr M. Khalil, Hattersheim; Dr M. Pohl, Köln; Dr G. Scharrer, Landsberg; Dr H. J. Taenzer, Cologne; Dr W. Vilmar, Nürnberg; Dr S. Winkelmann-Laue, Cologne; Dr C. Zamfirescu, Bad Homburg; Dr G. Zimmermann, Solingen.

**Hungary:** Prof F. Götz, Pécs; Dr L. Kissonedek, Budapest; Dr G. Nemere, Budapest; Prof I. Romics, Budapest.

**Poland:** Dr A. Antoniewicz, Warsaw; Prof A. Borowka, Warsaw; Prof A. Borkowski, Warsaw; Dr M. P. Rozniecki, Lask; Prof Z. Wolski, Bydgoszcz.

**Portugal:** Dr Z. Alves, Coimbra; Prof J. Branco, Lisboa; Prof M. Oliveira, Porto.

**Slovak Republic:** Dr J. Breza with Dr M. Miklosi, Bratislava; Dr J. Kliment with Dr J. Luptak, Martin; Dr J. Marencak, Skalica; Dr Valanky with Dr M. Baca, Kosice.

**Switzerland:** Dr T. Kovac, Le Châble.

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