ORAL IMMUNOTHERAPY OF RECURRENT URINARY TRACT INFECTIONS: A DOUBLE-BLIND PLACEBO-CONTROLLED MULTICENTER STUDY

C. C. SCHULMAN, A. CORBUSIER, H. MICHELS* AND H. J. TAENZER†

From the Department of Urology, Erasmus University Hospital, University of Brussels, Brussels, Belgium

ABSTRACT

We treated 166 patients suffering from recurrent urinary tract infections under double-blind conditions for 3 months with 1 capsule daily of either the immunostimulating bacterial extract (85) or a placebo (81), followed by a 3-month observation period without the test drugs. The bacterial extract exerted a significant beneficial curative action and long-term consolidative effect on the frequency of recurrent urinary tract infections with marked improvements in the characteristic signs and symptoms. It was significantly superior to placebo for the majority of the assessed parameters: number of recurrent urinary tract infections, bacteriuria, leukocyturia, erythrocyturia, nitrituria, albuminuria and casts in urine. Consumption of antibiotics, chemotherapeutics, urinary antiseptics or disinfectants was significantly less under active drug therapy compared to placebo. Tolerance was good with only 2 side effects reported in 2 patients (2%) in the active group compared to 11 among 5 (6%) in the placebo group. Therefore, the bacterial extract can be considered an efficient and well tolerated drug for the treatment of urinary tract infections, and their accompanying signs and symptoms, as well as for decreasing the risk of recurrences and the need for antibiotics and other antibacterial drugs.

KEY WORDS: urinary tract infections, bacteria, immunotherapy, placebo, recurrence

Urinary tract infections are generally caused by gram-negative organisms of enteric origin, in particular Escherichia coli, and they occur more frequently in patients with impaired defense mechanisms. The main present therapeutic approach involves the stimulation of the patient's own immune defenses. Moreover, their efficacy in the longterm treatment of chronic or recurrent urinary tract infections is somewhat less evident, especially since antibiotic-resistant bacterial strains. A different approach for the treatment of urinary tract infections involves the stimulation of the patient's own immune defenses against the pathogenic germs by oral administration of immunotherapeutics. One of these agents is a lyophilized proteinaceous extract obtained by fractionating the alkaline hydrolysate of selected E. coli strains. Electrophoresis shows a wide continuum of polypeptides of medium to high molecular weight (approximately 10 to 300 kD.). It is presented in capsule form, each containing as active principal 6 mg. of standardized immunostimulating fractions (Uro-Vaxom®, OM Laboratories, Geneva, Switzerland). The extract has been shown to protect animals against experimental infections with E. coli and Pseudomonas aeruginosa, and to stimulate macrophages and their phagocytic activity as well as B-lymphocytes and the activity of natural killer cells. It increases the level of different immunoglobulins in secretions and opposes the immunodepressive effect of certain antibiotics. Immunopharmacological studies with humans have shown that the extract increases the synthesis of serum interferon and of urine secretory IgA, as well as the number of active T-lymphocytes.

On the clinical level, several open and double-blind studies have demonstrated the therapeutic efficacy of the drug in urinary tract infections. These studies indicated in particular a significant decrease in the number of recurrent urinary tract infections, in bacteriuria and in other signs and symptoms, as well as in the need for concomitant antibiotic or chemotherapeutic treatments. All of these trials also demonstrated a good tolerance for the product, with a low incidence of minor and reversible side effects. Our double-blind placebo-controlled study was done to collect further information regarding the efficacy and safety of this immunostimulating bacterial extract in urinary tract infections in a fairly large patient collective.

MATERIALS AND METHODS

Study design. The study was a 6-month multicenter double-blind trial comparing the bacterial extract and placebo (3 months of treatment followed by 3 months of observation without test drugs) in patients with recurrent urinary tract infections. Each patient gave informed consent before entry. To be eligible for the study, the patient had to be an adult with a symptomatic recurring urinary tract infection in the acute phase with frequent past recurrences (at least 2 per year, history well known to the physician), and the infection had to be characterized by at least 10^5 bacteria per ml. in a midstream urine specimen or by at least 10^4 bacteria per ml. in a catheterized urine sample. Patients who were pregnant, or who presented with dysuria without positive bacteriological findings, established anomalies of the urinary tract with retention or lithiasis were excluded.

Drug administration. According to a centrally prepared randomization list, patients were treated under double-blind conditions for 3 months with 1 capsule daily of either the bacterial extract or placebo, taken in the morning on an empty stomach. The intake of any other immunostimulating drug was not allowed during the study. Concomitant treatment with antibiotics, chemotherapeutics, urinary antiseptics or disinfectants was allowed for the acute infection present at entry and for any eventual recurrence. The concomitant antibiotic or chemotherapeutic agent had to be selected between a broad-spectrum penicillin, a tetracycline, a nitrofurantoin derivative or cotrimoxazole. Any other antibiotic or chemotherapeutic agent could be...
prescribed only if judged necessary. All concomitant medications taken during the study had to be recorded.

**Evaluation of efficacy.** The examinations were scheduled at entry, after the initial antibiotic/chemotherapeutic or urinary antiseptic/disinfectant agent, after 3 and 6 months (mandatory visits), as well as at any eventual recurrence (intermediate visits). The main clinical evaluation criteria were the number of recurrent urinary tract infections (based on bacteriuria) and the consumption of antibiotics, chemotherapeutics, urinary antiseptics or disinfectants. The presence of dysuria was also assessed at each examination. Laboratory parameters evaluated as far as possible at each examination were bacteriuria, type of organism (according to the gram coloration, the organism identification was not mandatory), leukocyturia (less than 5, 5 to 10 or more than 10 leukocytes per field), erythrocyturia (negative or positive), albuminuria (negative, traces or positive), nitrituria (negative or positive) and casts in urine (negative or positive). The investigators assessed the curative effect of the test drugs supplementary to that of the antibiotic/chemotherapeutic or urinary antiseptic/disinfectant agent in the initial infection via the total as the consolidative long-term action until the end of the study.

**Evaluation of safety.** At each examination the investigator had to record any eventual side effect appearing throughout the study, with a detailed description of the nature, severity, duration, measures taken, evolution and relationship to test drugs.

**Statistical analysis.** Completed case report forms were sent for independent analysis to a biostatistician. Intergroup comparisons of qualitative variables and frequencies were performed with the chi-square, Cochran-Mantel or, for cell populations lower than 5, Kendall’s tau test. For quantitative variables, the analysis was performed with a parametric analysis of variance (ANOVA) or a nonparametric variance analysis (Kruskal-Wallis test). Student’s t test was used for comparison of the means. The level of statistical significance was set up at p ≤ 0.05.

**RESULTS**

**Patients.** Of the 166 recruited patients 85 were randomized to the bacterial extract and 81 to placebo groups. Because of too short a treatment duration (a few days) 3 patients were excluded from the extract group (1 for vertigo with visual troubles and 2 who did not return after the first visit for reasons unrelated to treatment) and 2 from the placebo group (pollakiuria and precipitant voiding in 1, and vertigo and vomiting in 1). One patient in the placebo group was excluded because of a major deviation (less than 10^3 bacteria per ml.) from the inclusion criterion of at least 10^6 bacteria per ml. Thus, 160 patients were included in the analysis of efficacy parameters (82 or extract, 69 women and 13 men aged 45.3 ± 2.0 years, and 78 on placebo, 65 women and 13 men aged 45.0 ± 1.8 years) and all 166 recruited patients in the safety analysis. During the study some data from 8 patients in the extract group and 10 of the placebo group were excluded from the efficacy analysis, mainly because they were recorded after the end of the study (obtained by telephone, requests of the patients) and 8 placebo patients, known but unrelated to therapy (change to another physician or hospitalization) in 2 extract-treated patients. In the absence of quantitative observations, the data on these 18 patients were not considered nor was their long-term efficacy assessment, thus accounting for the lower number of cases at month 6. A few minor deviations from the selection criteria were observed, such as initially 10^4 organisms or more per ml. instead of 10^6 or more (in 3 extract treated and 4 placebo patients) but they were not regarded as a reason for exclusion from the efficacy analysis. The 2 patient groups were homogeneous for all demographic and descriptive data, and baseline values of efficacy parameters as well as for the pretrial characteristics (number of concomitant diseases, and previous number of recurrent urinary tract infections and of anti-infectious treatments).

**Efficacy.** The main clinical evaluation criteria, that is the number of urinary recurrences and of concomitant anti-infectious drugs, showed a significantly better evolution in the active than in the placebo group. The number of recurrences with at least 10^3 bacteria per ml. was significantly lower in the extract group than in the placebo group during the 6 months of the trial (fig. 1) and this was even more marked during part 2. This was also the case for the number of recurrences with at least 10^6 bacteria per ml., totaling 59 in the extract group and 85 in the placebo group from the end of initial antibiotic/antiseptic cure to the end of month 3 (p < 0.01), 40 and 71, respectively, from month 4 to the end of month 6 (p < 0.001), and 99 and 155, respectively, for the total study duration (p < 0.0001, chi-square test). The mean number of recurrences with bacteriuria of at least 10^6 bacteria per ml. for the total study duration was 0.7 in the extract group and 1.5 in the placebo group, and for recurrences with bacteriuria of at least 10^6 organisms per ml. it was 1.2 compared to 2.0.

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 (fig. 2). A comparable evolution was observed for the intake of urinary antiseptics and disinfectants, which was significantly decreased (p < 0.05, Kruskal-Wallis test) dur-

![FIG. 1. Number of recurrent urinary tract infections (UTI) with 10^6 or more bacteria per ml. during study in bacterial extract (UV) and placebo (PB) groups. Statistical analysis was done with chi-square test.](image)

![FIG. 2. Consumption of antibiotics (AB) during study in bacterial extract (UV) and placebo (PL) groups (mean days ± standard deviation). Statistical analysis was done with Kruskal-Wallis test.](image)
Statistical analyses are given on top of columns (Cochran-Mantel test) treated cases than placebo-treated cases, which stresses a greater number of nil or low bacteriuria levels, respectively, at the end of the study, while they increased in the placebo group. Further, the consolidative efficacy of the extract, since only the placebo group (mean duration 8.1 ± 2.5 days). Statistical analysis of all data recorded during the study shows a highly significant difference in favor of the bacterial extract for both categories of concomitant drugs (p < 0.0001, chi-square test).

The symptom of dysuria, present in 96% of the patients at entry into the study, decreased more markedly in the extract group (11% at 3 and 6 months) than in the placebo group (20% at 3 and 6 months), approaching the limit of statistical significance (0.05 <p < 0.10, fig. 3). In regard to the different characteristic signs of urinary tract infections, they also showed important improvements in the active group with statistically significant differences in comparison to the placebo group (fig. 3). All signs and symptoms decreased markedly in both groups after the initial concomitant antimicrobial therapy and continued to decrease or even disappear in the extract group until the end of the study, while they increased in the placebo group. The detailed distribution of bacteriuria at the different examinations performed during the trial is given in table 1 and shows a greater number of nil or low bacteriuria levels, respectively, a smaller number of high bacteriuria levels in the extract group than in the placebo group toward the study end (p = 0.01, Cochran-Mantel test). The assessment of the 4 nonmandatory intermediate visits shows a lower number of examined extract-treated cases than placebo-treated cases, which stresses further the consolidative efficacy of the extract, since only patients with suspected urinary tract infections attended those visits. Organism identification was not mandatory but, nevertheless, it was performed in 85% of the cases. E. coli was responsible for the majority of infections with identified organisms (72%), followed by Proteus (7%), Enterococcus (5%), Staphylococcus (4%) and various organisms with no significant differences in regard to the evolution of the number of recurrent, persistence or change of the organism responsible for the initial infection during the study, nor for the occurrence of gram-negative, gram-positive or mixed gram-negative and gram-positive infection.

Based on the decrease in recurrent urinary tract infections and improvement in signs and symptoms, the efficacy assessments by the investigators showed a highly significant superiority of the bacterial extract over placebo for the curative action supplementary to that of the concomitant antibiotic or antiseptic in the initial infection considered to be certain or possible in 87% and 62% of the cases, respectively (p = 0.004) and for the long-term consolidative action until the end of the study considered to be certain or possible in 85% and 60% of the cases, respectively (p < 0.0001, chi-square test).

Safety. Clinical safety was good, with only 2 side effects reported in 2 patients (2%) in the extract group compared to 11 among 5 (6%) in the placebo group, leading to treatment withdrawal in 1 and 3 patients, respectively, without a significant intergroup difference (Kendall's tau test). The reported side effects were mainly vertigo and skin reaction in both groups (table 2).

**DISCUSSION**

The results of this double-blind placebo-controlled study clearly indicate that the bacterial extract has a beneficial and significant effect on the frequency of recurrent urinary tract infections with marked improvements in the typical signs and symptoms. This was accompanied by a significant decrease in the need for concomitant antibiotics, chemotherapeutics, urinary antiseptics or disinfectants. Since the consumption of these drugs was lower in the extract group than in the placebo group, it cannot account for the superior results recorded under the active drug. This is also revealed in the evolution of the different signs and symptoms, with a marked decrease in their frequency after the initial concomitant antimicrobial therapy given to all patients in both groups, and which continued to decrease or even disappear in the extract group, but increased in the placebo group despite its greater concomitant antimicrobial drug consumption.

It is now well recognized that antibiotics can interfere with

![Graph showing frequency of characteristic signs and symptoms at the four mandatory visits in bacterial extract (UV) and placebo (PL) groups.](image)
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The immune system of the patient, generally by suppressive action, has also been demonstrated at therapeutic doses and in clinical use. Such observations stress the importance of administering immunostimulating drugs to patients suffering from repeated urinary recurrences together or not with the state of nonreactivity or oral tolerance to ingested bacterial extract. However, it has been demonstrated that oral immunization generally leads to increased secretory IgA levels, which are essential for the prevention of urinary tract infections as well as for the diagnosis of the test extract. Our study clearly confirms the efficacy of the oral route in the study of recurrent urinary tract infections, and their accompanying signs and symptoms, improved in previous clinical trials. This mode of administration is also easier for the patients, resulting in higher compliance.

Regarding the parameter of bacteriuria 2 levels, that is at least 10^5 and 10^6 bacteria per ml. urine, were selected as definition for recurrent urinary tract infections during the study. This is in line with the newer concept of significant bacteriuria in which the limit of 10^6 or more bacteria per ml. has been replaced by a lower threshold. For both of these levels of bacteriuria a significantly better evolution of the number of recurrent urinary tract infections was observed in the active group.

The different favorable results recorded in our study, in particular the decrease in frequency of recurrent urinary tract infections and improvement in characteristic signs and symptoms, are reflected in the global assessment by the investigators of the curative and long-term consolidative efficiency of the test drug, which showed a highly significant superiority of the bacterial extract over placebo, and confirms those already observed in previous clinical trials.

Moreover, it is interesting to note that most of the improvements were more pronounced during part 2 of the trial, that is during the 3 months following administration of the test drugs, thus demonstrating further the long-term consolidative efficiency of the extract. Another noteworthy finding is the absence of a significant difference between the 2 treatment groups regarding the evolution of gram-negative, gram-positive or mixed infection, as well as the rate of persistence, recurrence or change of bacteria during the study, which indicates that the extract does not modify the spectrum of pathogenic organisms.

Clinical safety was good, since reported side effects were minimal in both groups and even less in the active than in the placebo group, with only 2 side effects reported in 2 extract treated patients versus 11 side effects in 5 placebo patients, leading to withdrawal in 1 and 3, respectively. Because in most patients the side effects occurred at the time of concomitant intake of antibiotics, chemotherapeutic, urinary antiseptic or disinfectant agents, the relationship between the observed side effect and the test drug is difficult to establish.

In conclusion, the bacterial extract can be considered as an efficient and well tolerated drug for the treatment of urinary tract infections, and their accompanying signs and symptoms.

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Drs. L. Denis, Antwerp; Ph. Laurent, R. Martens and D. Mucciante, Braine l'Alleud; J. Stevens, Brussels, and A. J. Thiry, Mons, Belgium, and N. Aboukoura, D. Berger and H. Berger, Köln, Germany, collaborated with this study. J. Cumps performed the statistics.

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