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Immunobiotherapy with Uro-Vaxom in Recurrent Urinary Tract Infection

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Summary—A series of 120 patients with recurrent urinary tract infection (UTI), all in acute recurrence at the start of the trial, were treated for 3 months under double-blind conditions with 1 capsule daily of either the immunobiotherapeutic product Uro-Vaxom (UV) or a placebo. They were then observed for 3 months without treatment. During the 6 months of the trial a significant decrease was noted in the UV group compared with the placebo group with respect to the number of recurrences of UTI, total consumption of antibiotics and chemotherapeutic agents, bacteriuria and dysuria. By the sixth month the UV patients were receiving no antibiotics. The final assessment was that UV was significantly more effective than the placebo. UV was well tolerated, with possible mild side effects in only 4 patients. During a further observation period of 5 months, patients who had received UV during the first period had fewer recurrences of UTI than those who had received placebo, confirming the long-term protective action of UV.

The treatment of chronic or recurrent urinary tract infection has become increasingly difficult since the emergence of antibiotic-resistant strains of organisms (Johnson, 1978). Over 50% of UTIs in young women recur within 12 months (Leski, 1983). The therapeutic value of activators of the body's immune defence mechanisms for therapy in such conditions is currently being explored (Fries, 1983). Uro-Vaxom (also known as Coli-Vaxom or OM-8930; manufactured by OM Laboratories, Meyrin, Geneva, Switzerland) is a new agent of this class which has been shown to increase the active T cell population and the proliferative responses to different mitogens (Rosenthal, 1986). It contains immunostimulating fractions extracted from *Escherichia coli* and is administered orally in a capsule. In a double-blind study involving 64 patients with recurrent UTI treated with UV for 3 months, Frey *et al.* (1986) noted a significant reduction in bacteriuria, dysuria, leucocyturia and the use of antibiotics and chemotherapeutic agents.

The aim of the present study was to investigate the frequency and severity of recurrences under double-blind conditions in a larger group of patients.

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Patients and Methods

Initially, 150 patients suffering from recurrent UTI were admitted to the trial. The inclusion criteria were: acute urinary infection with at least 10^5 organisms/ml in midstream urine or 10^4 organisms/ml in catheter urine at initial examination on CLED medium (for total organisms) or MacConkey medium (for gram-negative organisms) (Uribak, Biotechnik GmbH, Hamburg, Federal Republic of Germany) and at least 2 recurrences of UTI during the 6 months preceding the trial. The exclusion criteria were: dysuria without positive bacteriological findings, indwelling catheter, pregnancy, recurrent post-coital cystitis and urinary tract abnormalities. All patients gave informed consent before entering the trial.

Patients were randomly assigned to 3 months' treatment with 1 capsule daily of either UV or a placebo. A UV capsule contained 6 mg of immunostimulating fractions from *Escherichia coli* in lyophilised form. The treatment period was fol-

lowed by 3 months' observation without treatment. Antibiotics and chemotherapeutic agents were given as necessary throughout the trial. At the end of the 6-month trial, 57 patients (27 from the UV group and 30 from the placebo group) were kept under observation, independently of the study protocol, for about 5 months (average 24 weeks) and were given no treatment. Each patient had a medical examination at the beginning of the trial, at 3 and 6 months, 1 week after the end of initial antibiotic administration (usually about week 3) and at any possible recurrence of UTI. For the purposes of statistical analysis a recurrence was defined as the presence of bacteriuria with $\geqslant 10^4$ organisms/ml at any examination after the beginning of the trial. A record was made of concomitant treatment with antibiotics or chemotherapeutic agents, bacteriuria, dysuria, proteinuria, nitrituria, and numbers of urinary erythrocytes, leucocytes and casts, as well as patient compliance. The test products were evaluated in the light of their curative effects on the initial infection, their long-term consolidative efficacy, and their tolerance.

Of the initial 150 patients, 30 were not eligible for statistical analysis because of poor compliance (15 patients), a short observation period (1 patient), or factors related to the inclusion or exclusion criteria (14 patients). Thus 120 patients were statistically assessable: 61 of these (9 men and 52 women, mean age 51.2 ± 2.4 years) had received UV and 59 (8 men and 51 women, mean age 50.4 ± 2.3 years) had received placebo. Both groups were homogeneous with regard to age, sex, medical history (including number of UTI recurrences and use of antibiotics or chemotherapeutic agents) during the 6 months preceding the trial, and urinary characteristics at the beginning of the trial. All 150 patients were considered in the tolerance analysis. For comparison between treatment groups the 2-tail Student's t test was used for normally distributed variables, the Mann-Whitney U test and the Wilcoxon ranks W test for non-normally distributed variables and ordinal variables, and either the χ^2 test or Fisher's exact test (depending on the size of n) for frequencies. For comparison within groups the paired t test was used for continuous variables, the Wilcoxon test for ordinal variables, and McNemar's test for dichotomic variables.

Results

Recurrences

The mean number of recurrences, approximately 3.5 during the 6 months preceding the trial, was 0.82 in the UV group and 1.8 in the placebo group during the trial. The total number of recurrences was significantly lower in the UV group than in the placebo group, being respectively 38 and 63 ($P<0.05$) during the first 3 months, 12 and 41 ($P<0.01$) during the second 3 months (*i.e.* those without treatment) and 50 and 104 ($P<0.001$) for the total 6 months. The distribution of patients per number of recurrences was as follows (UV and placebo respectively): no recurrences (23, 10); 1 recurrence (27, 19); 2 recurrences (10, 10); 3 recurrences (1, 16); 4 recurrences (0, 3); 5 recurrences (0, 1) ($P<0.001$) (Fig. 1). In the additional follow-up study of 5 months without treatment after termination of the 6-month trial, recurrences occurred in only 10 of the 27 ex-UV patients, but in 20 of the 30 ex-placebo patients ($P<0.05$).

Antibiotics and chemotherapeutic agents

The total consumption of these products, assessed by the total number of days upon which they were administered, was approximately equal in the 2 groups during the first 3 weeks of the trial, but was significantly less in the UV than in the placebo group for the whole trial period ($P<0.001$) (Fig. 2).

The mean duration of antibiotic and chemotherapeutic use at the end of the third month (UV and placebo respectively) for antibiotics was 0.16 and 0.72 days ($P=0.08$) and for chemotherapeutic agents 0.44 and 1.02 days. At the end of the sixth

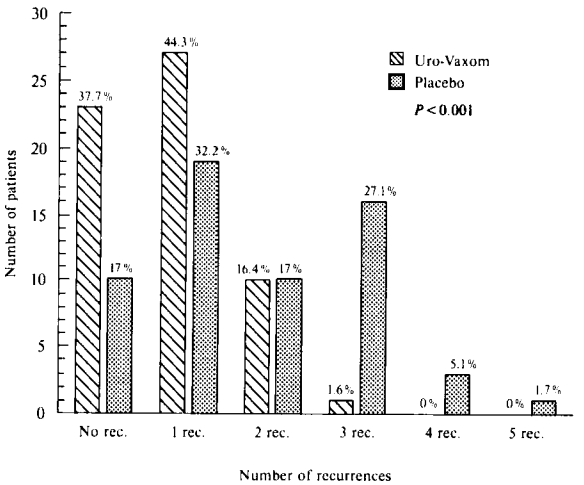

Fig. 1 Distribution of patients according to number of recurrences of infection during the 6-month trial period. A low incidence (0–1) predominated in the UV group and a higher incidence (3–5) in the placebo group.

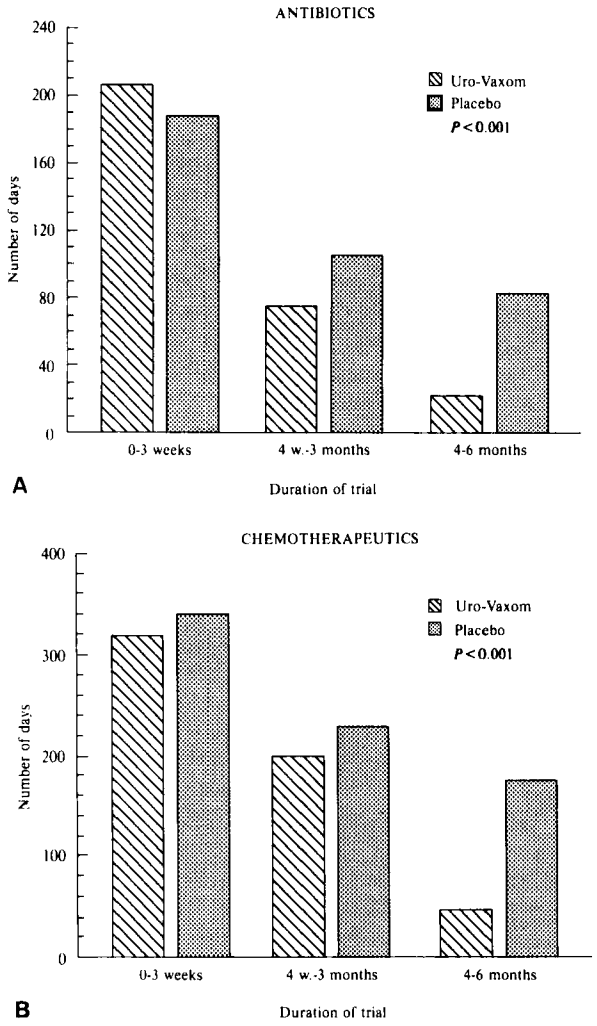

Fig. 2 Total consumption of antibiotics (A) and chemotherapeutic agents (B) expressed as number of days of adminstration during the 6-month trial period.

month it was 0 and 0.39 days (the absence of antibiotic in the UV group preventing the calculation of statistical significance) and 0.25 and 0.65 days.

Bacteriuria

Bacteriuria assessed on CLED medium (total number of organisms) was significantly less ($P<0.01$) in the UV group than in the placebo group at 3 and 6 months (Fig. 3).

Dysuria and nitrituria

At the beginning of the trial 93.4% of the UV patients and 91.5% of the placebo patients had dysuria, compared with 8.2 and 24.6% at the end of the sixth month ($P<0.05$). The corresponding figures for nitrituria were 83.6 and 86.4% and 4.9 and 15.8% ($P<0.05$).

Other urinary findings

Protein, erythrocytes, leucocytes and casts all decreased more in the UV than in the placebo patients, but the differences were not statistically significant.

Tolerance

Possible side effects were reported in 4 (5.4%) of the UV patients (pruritus, an allergic reaction leading to withdrawal of UV, diarrhoea, and headache with flushing) and in 2 (2.6%) of the placebo patients (repeated nausea, erythema).

Physicians' assessment

The efficacy of the test products with respect to their curative effect on the initial infection was judged to be "evident" in 31.1% of the UV patients and in 8.5% of the placebo patients, and to be "positive" (*i.e.* "evident" and "possible" efficacy taken together) in 95.1 and 72.9% respectively. Efficacy, in relation to long-term consolidative action assessed at 6 months, was judged as "evident" in 54.1% of the UV patients and 13.8% of the

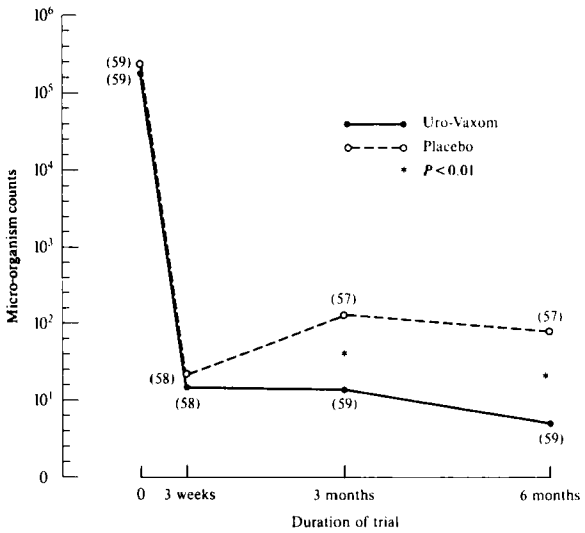

Fig. 3 Bacteriuria (CLED medium) in 118 patients (data not available for 2 patients) with urinary tract infection, half treated with Uro-Vaxom and half with placebo for 3 months and observed for a total of 6 months. Figures in parentheses are numbers of patients (2 placebo patients failed to complete the trial).

placebo patients and as "positive" in 95.1 and 60.3% respectively. The intergroup difference was highly significant ($P < 0.001$) for the assessments of both the curative and consolidative effect.

Discussion

This study has provided convincing evidence of the curative and consolidative effectiveness of UV in UTI as assessed by objective clinical criteria. Recurrences of infection, antibiotic and chemotherapeutic prescription, bacteriuria and the number of patients suffering from dysuria decreased in the UV patients in comparison with those treated by placebo.

The long-term protective action exerted by UV as a consequence of its stimulation of the body's immune system was confirmed by the significantly lower incidence of recurrences of UTI in the UV-treated patients observed without treatment for 5 months after the end of the 6-month trial, as compared with the placebo-treated patients. Thus, by consolidating the body's defences a 3-month course of UV reduces recurrences of UTI both during and after treatment.

The low incidence of side effects, even following prolonged administration, and the long-term protection against recurrence make UV a valuable complement to antibiotics, especially as the latter do not always prevent recurrent infection (Jameson, 1976; Stamm *et al.*, 1980), and may even, on repeated administration, lead to the emergence of antibiotic-resistant bacterial strains and untoward side effects (Braun *et al.*, 1981; Hannedouche *et al.*, 1983).

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