

Autovaccines for chronic urinary tract infections; ten years follow-up experience

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Abstract: *Introduction* This study describes the impact of a daily sublingual Probelte Pharma autovaccine ® program to prevent recurrent symptomatic UTI in non-responders adults to conventional antibiotic prophylaxis. *Material and Methods* Observational prospective open study including patients with recurrent UTI. A sublingual vaccine containing ethanol-killed bacteria extract from specific patient's uropathogenic strains were prepared from patient's semen or urine sample. The main outcome criteria were the number and severity of symptomatic/clinical UTI, specific antibiotic dosage and duration of use, adverse effects if any, and necessity to stop or change the antibiotic was noted. *Results* Thirty-two patients met inclusion/exclusion criteria (17 men, 53.1%; 15 women, 46.8%). After 10 years follow up under autovaccine, the number of positive urine cultures decreased from 100% to 87% (P >0.05) and no patient take any curative antibiotics. *Conclusion* Probelte Pharma autovaccine ® provides a reduction in symptomatic repeated UTI and decrease the use of antibiotics with a good tolerance.

Keywords: Chronic Urinary Tract Infections, Vaccine, Sublingual, Treatment

1. Introduction

One in two women develop a urinary tract infection (UTI) at least once in her life. The young and sexually active are more common affected, but it is also seen in elderly, postmenopausal women. The likelihood of recurrence is high in women; 50–80% of women will suffer at least one episode of UTI in their lifetime and 20–50% of women will have recurrent episodes (1). Recurrent UTIs secondary to reinfection are more common than relapse or persistent infections and account for 80% of recurrent UTIs (2). There are no studies were the incidence of recurrent UTI in men was evaluated but it is known that bladder outlet obstruction (BOO) and significative residual post voiding are predisponing factors to UTI in men (3)

While antibiotics are effective in treating acute infections and are the primary means of prophylaxis in patients with recurrent infections, increasing concern about the use or misuse of antibiotics, resulting in increasing resistance, has

high-lighted the need for rational pharmacotherapy of common infections in general practice (4). As an alternative to prophylactic antibiotics, several vaccines have been developed and have undergone clinical testing with good results (5).

This study describes the impact of a daily sublingual Probelte Pharma Autovaccine ® program to prevent recurrent symptomatic UTI in non-responders adults to conventional antibiotic prophylaxis.

2. Material and Methods

Observational prospective open study including patients with recurrent UTI. Clinical Investigation Comitee (CIC) approved this study.

Patients with repeated urinary tract infections (>2/1 year or >1 during 6months), confirmed urine culture with >10² (for repeated cystitis) or >10³ (for repeated pyelonephritis, orchyepydidimitis or prostatitis) colony-forming units/mL

(CFU/ml) of uropathogen in a mid-stream sample of urine (6) and antibiotic prophylaxis treatment for one year. Specific exclusion criteria were anatomical or functional abnormalities of urinary tract (urological tumor, urolithiasis, neurogenic bladder, interstitial cystitis, kidney stones, indwelling catheter urinary diversion and vesicoureteral reflux (VUR), excluded after cistouretrography) and systemic immunosuppression. All men and women had a urologic evaluation consisting of urinary cytology, excretory urogram or renal ultrasound, urodynamics, and cystoscopy.

Bacterial germs were isolated from urine or semen from each patient [8]. Each bacteria had its preparation method, for example, for *E. Coli*: A complex composed of the periplasmic chaperones FimC and FimH in a 1 : 1 equimolar ratio was expressed in *E. coli* K12 strain C600 extracted from the periplasm and was purified to 99% purity by previously published methods [9]. We used ethanol to inactivate extract from specific patient's uropathogenic strains. Patients collected their own sample and prepared it for sending to pharmaceutical laboratory

(introduce the urine or semen, if it was required, in a microbiological culture medium provided by the laboratory). After 3 weeks, autovaccine reaches to patient. Each patient received 3 months daily-autovaccine and at monthly visit we evaluated patient's symptoms, and urine cultures. Clinical infection was established according to specific guidelines (6). The main outcome criteria were the number and severity of symptomatic/clinical UTI, specific antibiotic dosage and duration of use, adverse effects if any, and necessity to stop or change the antibiotic was noted. Intervals until initial reinfections, average number of infections, and proportion remaining infection free at 1, 3, 5, 7 and 10 years were collected. Urinary and semen (in men) samples were collected for microbiological and non microbiological analysis. Demographics of patients were evaluated through descriptive statistics, expressed in terms of mean and standard deviation (sd). Statistical analysis was performed with the SPSS 15 V system. Data was analyzed with parametric Student's *t*-test.

3. Results

Table 1. Demographics of patients; DM: diabetes mellitus;

	Men	Women
Number patients (n° p)	17	15
Age	48,6 sd 12,6	51,2 sd 10,1
Mean UTIs in previous 12 months	8.17 sd 3,6	9,33 sd 4,2
N° p sexually active	17	15
Comorbidity	2 patients DM; 1 patient dislipemia	2 patients DM; 2 patients arterial hypertension
UTI previous autovaccine	16 patients: prostatitis 1 patient: orchitis	14 patients: cystitis 1 patient: pyelonephritis
Multimicrobial UTI	2 patients 12 patients: Levofloxacin	0 patients 10 patients: Ciprofloxacin
Antibiotics in previous 12 months	3 patients: Doxycycline 2 patients: Cephuroxime	3 patients: Fosfomicin 2 patients: TMX/SMX

Table 2. Evolution of UTI, antibiotic consumption and bacteriological results

	Previous autovaccine	10 at years follow up	P
Number UTIs/patient	7,6 sd 5,3; Men: 7,17 sd 3,6 Women: 9,33 sd 4,2	0 Men 0 Women	0.003
Bacteria	Men: E. Coli 5 patients; Klebsiella 4 patients; Proteus 3 patients E. Coli+Proteus spp; E. coli+Klebsiella spp; Citrobacter; E. Fecalis; S. epidermidis: 1 patient respectively Women: E. Coli 14 patients; Proteus spp 1 patient	Men: E. coli 11 patients Proteus spp 2 patients Klebsiella 2 patients Women: E. Coli 13 patients	0.0027 0.0003
Positive urine culture	17 Men 15 Women	15 Men (88.6%) 13 Women (86.6%)	0.067 0.062
Antibiotic treatment	17 Men 15 women	0 Men 0 Women	0.004

Thirty-two patients met inclusion/exclusion criteria (17 men, 53.1%; 15 women, 46.8%). Mean age was 43.8 years (sd 13.9). Before the autovaccine program, patients had an average of 7.6 (sd 5.3) UTI per year: orchitis (1 patient), prostatitis (16 patients), acute pyelonephritis (2 patients) and acute cystitis (13 patients). All patients were sexually active. Mean UTI in previous 12 months were 8.17 (sd 3.6) in men and 9.33 (sd 4.2) in women. Previous to

autovaccine, all patients underwent antibiotic prophylaxis with levofloxacin, doxycycline, cephuroxime (12, 3 and 2 men respectively) and ciprofloxacin, fosfomicin and TMX/SMX (10, 3 and 2 women respectively). Demographics of patients are shown in table 1.

Previous to autovaccine, infection was monomicrobial in 30/32 patients and mixed in only 2 patients. The principal microorganisms isolated in urine cultures before

autovaccine included *E. coli* 59.4%, *Klebsiella* 12.5%, *Proteus* 3%, *Citrobacter* 3%, *E. Fecalis* 3%, *S. Epidermidis* 3%, *P. Aeruginosa* 3% and *E. Cloacae* 3%. Urinary analysis revealed micro-hematuria in 24/32 patients (10 men and 14 women) and leucocyturia in 32/32 patients.

After 10 years follow up under autovaccine, the number of positive urine cultures decreased from 100% to 87% ($P > 0.05$). A significant evolution of bacterial colonization was noted. The bacteria isolated from urine samples at the end of the follow-up period were: *E. Coli*. 85.7%, *E. Fecalis* 7.1% and *Proteus* 7.1% patients with positive urine cultures. Urinary analysis showed no hematuria in men and only in 3/15 women and leucocyturia in 2/17 men and 2/15 women.

Number and type of UTI, bacteriological results and king's health questionnaire are shown in table 2 and III. After autovaccine a 10-year follow-up there was no patient with symptomatic UTI. There was a significant decrease in antimicrobial usage linked to the dramatic decrease in the incidence of UTI. (Table 2). After the autovaccine programs no patient took any curative antibiotics. Evolution of urinary cultures results and UTIs episodes are shown in figures 1-2.

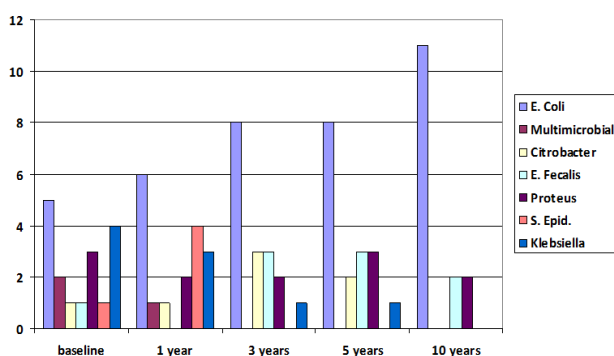


Figure 1. Evolution of urinary cultures in men

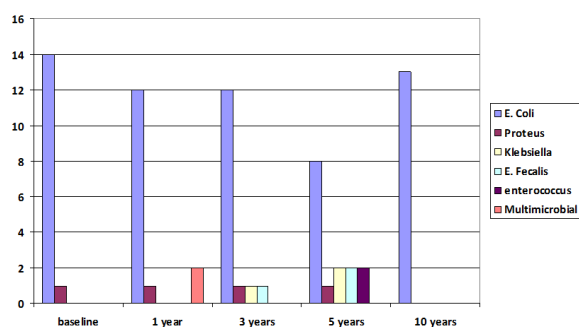


Figure 2. Evolution of urinary cultures in women

4. Discussion

In this prospective, observational study a novel approach to the prevention and treatment of refractory antibiotic therapy prophylaxis UTI patients was investigated.

Sublingual immunotherapy can be self-administered at home, requiring fewer clinic visits. The efficacy of sublingual administration is now well documented, with

several phase III studies showing success with both adults and children as young as 5 years of age (7), and it has been proved to increase antibodies presence in every mucosa, including urogenital (8). The vaccine tested previously (9), and, in the current study, contains a self-specific uropathogen ethanol-killed bacteria patient extract administered as a mucosal immunogen. This approach has the advantage of inducing specific primarily immunogenic response, thereby reducing potential colonization of the bladder with uropathogens.

Recurrent UTI may be caused by persisting bacteria, despite initial clinically successful therapy or even sterilization of the urine. A second course, longer than the standard three days, of a first-choice drug has been proposed for treatment of UTI recurring shortly after an initial episode (10,11). Long-term, low-dose antibiotic prophylaxis, post-coital antibiotics and self-start therapy have all been demonstrated to be effective in managing recurrent uncomplicated UTIs in women. However, in view of the emergence of antibiotic resistance and attenuation of the host response, there is limitation in long-term antibiotic use (12,13). In this study we present an alternative treatment for recurrent UTI in long term antibiotic therapy prophylaxis non-responding patients.

The idea of employing bacterial immune stimulants in order to reduce recurrent UTI was born some 40 years ago (14) but only in recent years has a better understanding of the innate immune system provided a solid rationale for such immune stimulants.

We observed a significant reduction in the number of symptomatic UTI ($p=0.003$). This is probably due to the heavy immunogenic response of the autovaccine administered once daily during 3 months, which stimulates infection-combating, circulating elements within the lymphoid tissue and that the target organ envisioned is immunocompetent in order to translate adequately such a stimulus into an efficient response. A similar method using Uro-Vaxom® (OM Pharma, Geneva, Switzerland), that is a purified *E. coli* extract that is administered orally, has also been shown to be effective(15). A meta-analysis was performed on five studies conducted over the last decade to demonstrate a positive effect for the drug Uro-Vaxom compared with Placebo in double-blind studies in patients with urinary tract infection (601 women), in all studies, the Uro-Vaxom group was statistically significant and clinically relevant superior to control with respect to the reduction of the frequency of UTIs and to dysuria, bacteriuria and leucocyturia(16) Despite the mechanism of recurrent UTI in women and men are very different (17,18) in our study autovaccines reduces number of symptomatic UTI episodes in men and women at long time follow-up.

The efficacy demonstrated by vaginal suppositories prepared using Urovac™ (a vaccine containing heat-killed bacteria from 10 human uropathogenic strains) in 3 independent phase 2 clinical trials indicates that it may provide an alternative to long-term antibiotic prophylaxis for recurrent UTIs in susceptible women. (19-21). In our

study we used the sublingual as route of administration. It is known that mucosal vaccines also elicit minimal adverse effects. Mucosal membranes of the respiratory and intestinal tracts are exposed daily to antigenic substances, which induce specific humoral as well as cell-mediated immune responses not only at the site of the stimulation-mucosa-associated lymphoid tissues, but also in the draining lymph nodes, spleen and bone marrow. This idea encourages the attempt to investigate the oral route. Fanta *et al.* (22) after their sublingual spit immunotherapy investigation concluded that sublingual treatment leads to systemic changes in immunoreactivity to the administered allergen. The sublingual approach seems to offer the advantage both of sublingual and intestinal administration, thus it was the preferred method in our study.

The median age of the patients was 43.8 years, indicating a trend towards younger patients, which is probably a reasonable reflection of typical age distribution in the incidence of UTI

Almost, the data presented here provided a statistically significant reduction in medication symptomatic UTI.

Compliance of our patients to sublingual immunotherapy was very good and no premature termination of treatment due to side effects was found.

5. Conclusions

The results of this observational prospective study allow us to conclude that a 10-year treatment with Probelte Pharma Autovaccine® improves a significant reduction in the number of symptomatic UTI and use of antibiotic therapy in patients with recurrent UTI with no adverse effects reported.

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