American Journal of Life Sciences
2014; 2(6-3): 13-17
Published online November 23, 2014 (http://www.sciencepublishinggroup.com/j/ajls)
doi: 10.11648/j.ajls.s.2014020603.13
ISSN: 2328-5702 (Print); ISSN: 2328-5737 (Online)

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

Gallego-Vilar Daniel[1], Sanchis-Verdu Laura[2], Beltran Persiva Jose[1], Cuñat-Albert Enrique[2], Cervello-Grima Enrique[1], Gallego-Gomez Juan[2], Perez-Mestre Mateo[3]

[1]FED, Department of Urology, Castellon Provincial Hospital, Castellon, Spain
[2]Department of Urology, Castellon General Hospital, Castellon, Spain
[3]Department of Urology, Castellon Provincial Hospital, Castellon, Spain

Email address:
dagalvi@hotmail.com (Gallego-Vilar D.)

To cite this article:
Gallego-Vilar Daniel, Sanchis-Verdu Laura, Beltran Persiva Jose, Cuñat-Albert Enrique, Cervello-Grima Enrique, Gallego-Gomez Juan, Perez-Mestre Mateo. Autovaccines for Chronic Urinary Tract Infections; Ten Years Follow-Up Experience. *American Journal of Life Sciences.* Special Issue: Microbiology Research. Vol. 2, No. 6-3, 2014, pp. 13-17. doi: 10.11648/j.ajls.s.2014020603.13

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 descrease 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 predisponding 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 $>10^2$ (for repeated cystitis) or $>10^3$ (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 cistourethrography) and systemic immunosuppression. All men and women had a urologic evaluation consisting of urinary cytology, excretory urogram or renal ultrasound, urodynamics, and cystoscopy.

Bacterial germen were isolated from uryne or semen from each patient [8]. Each bacteria had it preparation method, for exemple, 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´t- test.

3. Results

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

	Men	**Women**
Number patients (nº 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
Nº p sexually active	17	15
Comorbidity	2 patients DM; 1 patient dislipemia	2 patients DM; 2 patients arterial hypertension
UTI previous autovaccine	16 patients: prostatytis 1 patient: orchitis	14 patients: cystitis 1 patient: pyelonephritis
Multimicrobial UTI	2 patients	0 patients
Antibiotics in previous 12 months	12 patients: Levofloxacin 3 patients: Doxycycline 2 patients: Cephuroxime	10 patients: Ciprofloxacin 3 patients: Fosfomycin 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	Men: E. coli 11 patients Proteus spp 2 patients Klebsiella 2 patients	0.0027
	Women: E. Coli 14 patients; Proteus spp 1 patient	Women: E. Coli 13 patients	0.0003
Positive urine culture	17 Men	15 Men (88.6%)	0.067
	15 Women	13 Women (86.6%)	0.062
Antibiotic treatment	17 Men	0 Men	0.004
	15 women	0 Women	

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, doxicicline, cephuroxime (12, 3 and 2 men respectively) and ciprofloxacine, fosfomycin 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.

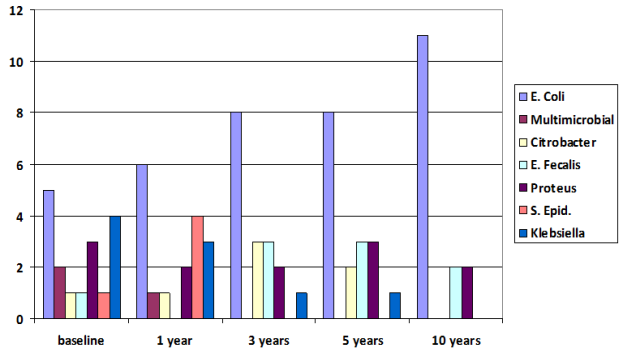

Figure 1. *Evolution of urinary cultures in men*

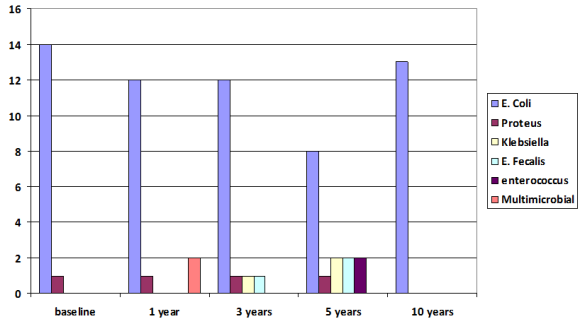

Figure 2. *Evolution of urinary cultures in women*

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 inmunogenic 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 inmunogenic 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 mecanism 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 UrovacTM (a vaccine containing heat-killed bacteria from 10 human uro- pathogenic 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 adverses effects reported.

References

[1] Dielubanza EJ, Schaeffer AJ. Urinary tract infections in women. Med Clin North Am. 2011 Jan;95(1):27-41.

[2] Williams DH, Schaeffer AJ. Current concepts in urinary tract infections. Minerva Urol Nefrol. 2004 Mar;56(1):15-31.

[3] Brookman et al. Association between residual urinary volumen and urinary tract infection: prospective trial in 225 male patients. Urologe A. 2010 Sep; 49(9): 1163-8

[4] Schaeffer AJ, Stuppy BA. Efficacy and safety of self-start therapy in women with recurrent urinary tract infections. J Urol. 1999 Jan;161(1):207-11

[5] Hopkins WJ and Uehling DT: Vaccine development for the prevention of urinary tract infections. Curr Infect Dis Rep 2002; 4: 509.

[6] Naber KG, Bergman B, Bishop MC, Bjerklund-Johansen TE, Botto H, Lobel B, Jinenez Cruz F, Selvaggi FP; Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). EAU guidelines for the management of urinary and male genital tract infections. Urinary Tract Infection (UTI) Working Group of the Health Care Office (HCO) of the European Association of Urology (EAU). Eur Urol. 2001 Nov;40(5):576-88.

[7] Dahl R, Kapp A, Colombo G, de Monchy JGR, Rak S, Emminger W, Fernandez Rivas M, Ribel M, Durham SR: Efficacy and safety of sublingual immunotherapy with grass al- lergen tablets for seasonal allergic rhinocon- junctivitis. J Allergy Clin Immunol 2006; 118:434–440.

[8] Didier A, Malling HJ, Worm M, Horak F, Jager S, Montagut A, Andre C, de Beaumont O, Melac M: Optimal dose, efficacy, and safety of once-daily sublingual immuno- therapy with a 5-grass pollen tablet for sea- sonal allergic rhinitis. J Allergy Clin Immu- nol 2007;120:1338–1345.

[9] Gallego Vilar D, Povo Martin I, Gimeno Argente V, Bosquet Sanz M, Garcia Torreles M, Martinez Ramos D, Gallego Gomez J, et al. Autovaccines for urinary tract infections. Urod Aplic. 2008. Vol21;2:99-104.

[10] Wagenlehner FM, Schmiemann G, Hoyme U, Fünfstück R, Hummers-Pradier E, Kaase M, Knieh E, Selbach I, Sester U, Vahlensieck W, Watermann D, Naber KG. S3-guideline for uncomplicated urinary tract infections - treatment guidelines compliance. Med Monatsschr Pharm. 2011 May;34(5):164-8.

[11] Hooton TM. Recurrent urinary tract infection in women. Int J Antimi- crob Agents 2001;17:259–68.

[12] Kahlmeter GJ. An international survey of the antimicrobial suscep- tibility of pathogens from uncomplicated urinary tract infections: the ECO.SENS Project. J Antimicrob Chemother 2003;51:69– 76.

[13] Karlowsky JA, Jones ME, Thonsberrry C, Friedland IR, Sahm DF. Trends in antimicrobial susceptibilities among Enterobacteriaceae iso- lated from hospitalized patients in the United States from 1998 to 2001. Antimicrob Agents Chemother 2003;47:1672–80.

[14] Westenfelder M. Lipoid A, a factor in the pathogenesis of chronic pyelonephritis. Experimental and clinical studies of a lipoid A dependent pathological immune reaction and they have been used, rather empirically, to prevent recurrent infections in the non-immunocompromised host. Fortschr Med. 1979 Feb 8;97(6):245-8.

[15] Ha US, Cho YH. Immunostimulation with Escherichia coli extract: prevention of recurrent urinary tract infections. Int J Antimicrob Agents. 2008 Feb;31 Suppl 1:S63-7.

[16] Bauer HW, Rahlfs VW, Lauener PA, Blessmann GS. Prevention of recurrent urinary tract infections with immuno-active E. coli fractions: a meta-analysis of five placebo-controlled double-blind studies. Int J Antimicrob Agents. 2002 Jun;19(6):451-6.

[17] Thomas M. Hooton. Recurrent urinay tract infections in women. International journal of Antimicrobial agents. 17 2001; 259-268

[18] Caron F. [Diagnosis and treatment of community-acquired urinary tract infections in adults: what has changed. Comments on the 2008 guidelines of the French Health Products Safety Agency (AFSSAPS)]. Presse Med. 2010 Jan;39(1):42-8.

[19] Uehling DT, Hopkins WJ, Balish E, Xing YN and Heisey DM: Vaginal mucosal immunization for recurrent urinary tract infection: phase II clinical trial. J Urol 1997; 157: 2049.

[20] Hopkins WJ, Elkahwaji J, Beierle LM, Leverson GE, Uehling DT. Vaginal mucosal vaccine for recurrent urinary tract infections in women: results of a phase 2 clinical trial. J Urol. 2007 Apr;177(4):1349-53.

[21] Uehling DT, Hopkins WJ, Beierle LM, Kryger JV, Heisey DM. Vaginal mucosal immunization for recurrent urinary tract infection: extended phase II clinical trial. J Infect Dis. 2001 Mar 1;183 Suppl 1:S81-3.

[22] Fanta C, Bohle B, Hirt W, Siemann U, Horak F, Kraft D, Ebner H, Ebner C. Systemic immunological changes induced by administration of grass pollen allergens via the oral mucosa during sublingual immunotherapy. Int Arch Allergy Immunol. 1999 Nov;120(3):218-24.