available at www.sciencedirect.com
journal homepage: www.europeanurology.com

European Association of Urology

Recurrent Urinary Tract Infections: Uro-Vaxom®, a New Alternative

Francisco Cruz[a,*], *Miriam Dambros*[b], *Kurt G. Naber*[c], *Hartwig W. Bauer*[d], *Gabriel Cozma*[e]

[a] *Department of Urology, Hospital S. João, Porto, Portugal*
[b] *Division of Urology, State University of Campinas-UNICAMP, São Paulo, Brazil*
[c] *Technical University of Munich, School of Medicine, Munich, Germany*
[d] *Department of Urology, Ludwig-Maximilian-University, Munich, Germany*
[e] *OM PHARMA, Geneva, Switzerland*

Article info

Keywords:
Antibacterial agents
Cystitis
Immunostimulant
Microbial drug resistance
OM-89
Prophylaxis
Recurrence
Urinary tract infections
Uro-Vaxom

Abstract

Context: Acute uncomplicated cystitis is generally treated with short-term antibiotic therapy. However, recurrence of lower urinary tract infections (UTIs) is very common, especially in premenopausal women. These recurrent infections considerably affect a patient's quality of life and have a huge financial and economic impact on society. Therefore, prevention of UTI recurrence is highly important.
Objective: To provide an overview of the state of the art and the current controversies on the prophylaxis of recurrent UTIs.
Evidence acquisition: This manuscript is based on presentations given at a satellite symposium held at the 2nd World Congress on Controversies in Urology (CURy) in Lisbon, Portugal. Data were retrieved from recent review papers, original papers, and abstracts on recurrent UTIs.
Evidence synthesis: Currently, antibiotic prophylaxis is recommended as a first-line strategy for the prevention of recurrent UTIs in the European Association of Urology guidelines. However, more and more uropathogens become resistant to certain types of antimicrobials. Hence, alternative prophylactic strategies are gaining importance. Oral administration of immunoactive *Escherichia coli* (*E. coli*) fractions (Uro-Vaxom®) is one of these methods. Our understanding of its mechanism of action has considerably grown over the past 20 yr. In several double-blind, placebo-controlled studies, oral immunostimulation with *E. coli* extracts significantly reduced recurrent UTIs compared with placebo. Moreover, this strategy was well tolerated. Two new Uro-Vaxom studies have been initiated to gather more data on the long-term efficacy, the treatment regimen, and the mechanism of action of this immunostimulant and to find broader indications for this therapy.
Conclusions: Although scientific and clinical data on oral immunostimulation with *E. coli* fractions have increased significantly, more studies are needed to provide convincing evidence that this strategy is equally effective as antibiotic prophylaxis for the prevention of recurrent cystitis.

* Corresponding author. Department of Urology, Hospital Sao João, Porto, Portugal.
Tel. +351 2 5091468; Fax: +351 2 5505728.
E-mail address: cruzfjmr@med.up.pt (F. Cruz).

1569-9056/$ – see front matter doi:10.1016/j.eursup.2009.07.002

1. Introduction

Urinary tract infections (UTIs) are among the most common bacterial infections in humans. They occur much more frequently in women than in men. About 40–50% of women will experience at least one UTI during their lifetime [1]. According to their site of manifestation, these infections are classified as cystitis (bladder), prostatitis (prostate), urethritis (urethra), or pyelonephritis (kidney). Among these UTIs, cystitis is the most common. In its uncomplicated form, it is a benign infection that is limited to the urine and the bladder wall and is not accompanied by fever or tissue alterations. This condition is particularly frequent in young women. In contrast, when cystitis is complicated, other organs may be involved as well (kidneys, prostate, epididymis, testes). Such infection usually affects patients with a debilitated status, that is, patients with urologic disorders (obstructive malformations, postvoid residual), neurologic disorders (neurologic bladder, functional troubles), or systemic disorders (diabetes, immunosuppression). Hence, complicated cystitis is more common in men, children, and elderly people.

In >80% of acute, uncomplicated cystitis cases, *Enterobacteriaceae* and *Escherichia coli* (*E. coli*) in particular are the responsible pathogens [2]. These bacteria cause infections by adhering to, invading, and replicating in the umbrella cells of the bladder epithelium [3]. *E. coli* replication is facilitated by inflammation, leading to increased bacterial survival and invasion of the deeper layers of the urothelium. Consequently, these urothelial cells become reservoirs in which pathogens persist in a quiescent state. These bacterial reservoirs may be the source of recurrent UTIs.

UTIs are defined as recurrent if there have been at least two acute episodes in the past 6 mo or at least three infections in the past 12 mo [4]. They are quite common: 20–30% of adult women will have recurrence within 3–4 mo after an initial UTI [1]. About 10–20% of women are even experiencing recurrent UTIs during their entire life span. Several factors are known to increase a patient's susceptibility to recurrent UTIs, such as recent use of antibiotics, congenital abnormalities, urinary obstruction, prior history of UTIs, diabetes, incontinence, and urologic surgery [1]. In addition, sexual intercourse and the use of a diaphragm, condom, or spermicides for contraception are major risk factors for recurrent UTIs in premenopausal women [5]. Conversely, in postmenopausal women, a lack of oestrogen, which protects the vagina from colonisation by *Enterobacteriaceae* by stimulating the growth of vaginal *Lactobacilli*, is associated with an increased likelihood of UTIs [6].

Although a single episode of acute, uncomplicated cystitis is considered a benign condition, recurrent UTIs have a considerable impact on a woman's quality of life. Indeed, each episode of acute UTI in young women is associated with about 6.1 d of symptoms, 2.4 d of restricted activities, 1.2 d of inability to attend classes or work, and 0.4 d of bed rest [1]. Moreover, these infections place an enormous financial and economic burden on society. Consequently, treatment of uncomplicated cystitis should aim further than the disappearance of acute clinical symptoms. It should also focus on the prevention of UTI recurrences.

2. Evidence acquisition

This paper is based on presentations given at a satellite symposium on recurrent UTIs held during the 2nd World Congress on Controversies in Urology (CURy) on 6 February 2009 in Lisbon, Portugal. Data were retrieved from recent review articles, original articles, and abstracts on recurrent UTIs.

3. Evidence synthesis

3.1. *European Association of Urology guidelines on recurrent urinary tract infections*

The guidelines of the European Association of Urology (EAU) [4] stipulate that short-term antibiotic therapy is the treatment of choice for each episode of acute, uncomplicated cystitis (Fig. 1). This therapy effectively leads to a rapid disappearance of clinical symptoms and a reduction of morbidity. Short-term treatment has several advantages over longer use of antibiotics. It is associated with an improved compliance, lower costs, and fewer adverse events. Most important, short-term administration of antibiotics also has a lower impact on periurethral, vaginal, and rectal flora compared with longer treatment because it exerts a lower selection pressure for antibiotic-resistant strains.

Uropathogen resistance has indeed become a serious problem for certain types of antimicrobials. In the recent Antimicrobial Resistance Epidemiology in Females with Cystitis (ARESC) study in nine European countries and Brazil, the susceptibility of uropathogens isolated from women with symptoms of uncomplicated cystitis to nine antibiotic substances was evaluated. About 30% and 50% of all isolated uropathogens were resistant to trimethoprim-sulphamethoxazole (TMP-SMX, cotrimoxazole) and ampicillin, respectively [2]. In women infected with such TMP-SMX–resistant pathogens, the rates of microbiologic

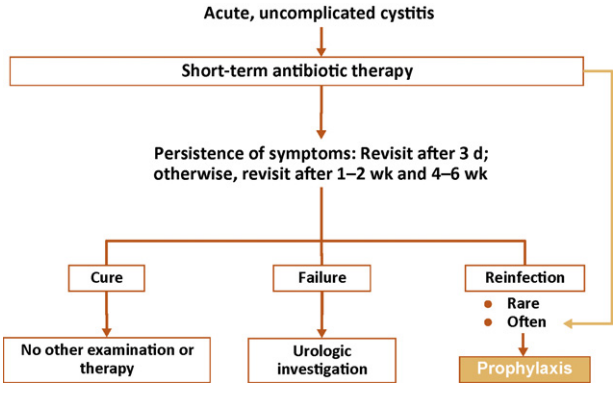

Fig. 1 – Schematic overview of the management of acute, uncomplicated cystitis according to the European Association of Urology guidelines [4]. Short-term antibiotic therapy is the treatment of choice for acute, uncomplicated cystitis, while prophylaxis is recommended to prevent recurrent infections.

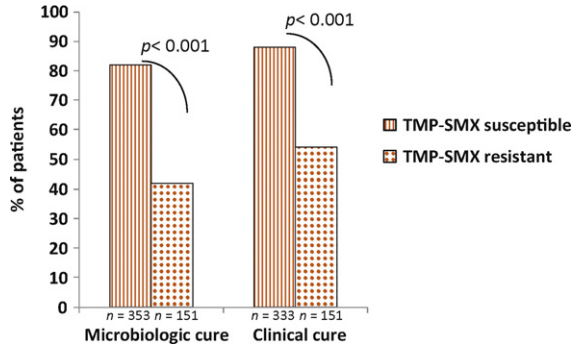

Fig. 2 – Urinary tract infection with trimethoprim-sulphamethoxazole (TMP-SMX)–resistant uropathogens is associated with a higher rate of treatment failure than infection with TMP-SMX–susceptible uropathogens. Microbiologic cure and clinical cure at 5–9 d after cessation of TMP-SMX therapy was assessed in premenopausal women with acute, uncomplicated cystitis [7]. Cure rates were compared between women infected with TMP-SMX–susceptible pathogens and women infected with TMP-SMX–resistant pathogens.

and clinical failure were significantly higher than in women infected with TMP-SMX–susceptible pathogens (Fig. 2) [7]. Consequently, these antimicrobial agents are not recommended as first-line drugs for the treatment of acute, uncomplicated cystitis [4]. Instead, fosfomycin, mecillinam, and nitrofurantoin should be preferred for empiric therapy. Indeed, despite the wide variation in susceptibility rates from country to country, >90% of *E. coli* cultures were susceptible to these antimicrobial agents in each country tested [2]. For other antibiotics such as trimethoprim and fluoroquinolones, the local rate of uropathogen resistance should be considered before prescribing them as first-line drugs for empiric treatment of acute, uncomplicated cystitis [4].

Persistent bacteriuria after 2–3 d or recurrence within 2 wk despite short-term antibiotic therapy might indicate the involvement of the underlying parenchyma or an underlying complicating factor. Hence, urologic investigation is required (Fig. 1). Alternatively, symptoms that resolve after antimicrobial treatment but recur after 2 wk suggest bacterial reinfection. To prevent the latter event, prophylactic measures are required.

Currently, antibiotic prophylaxis is recommended in the EAU guidelines as the first-line option for the prevention of recurrent cystitis [4]. Using this strategy, the number of patients with at least one microbial recurrence can be reduced from 65.5% (for placebo-treated patients) to 12.3% of patients [8]. Three different antimicrobial regimens have shown their efficacy: long-term, low-dose prophylactic antimicrobials taken at bedtime; postcoital reduced dose of antimicrobials for women in whom UTI episodes are associated with sexual intercourse; and patient-initiated treatment in well-informed young women. The standard agents for antimicrobial prophylaxis are nitrofurantoin (50–100 mg/d), trimethoprim (50–100 mg/d), TMP-SMX (40/200 mg/d or three times per week), and fosfomycin trometamol (3 g per 10 d) [4].

Given this limited number of antimicrobial agents suitable for the prophylaxis of recurrent uncomplicated cystitis and given the growing number of multi-drug-resistant uropathogens, alternative strategies have to be envisaged. In postmenopausal women, local administration of oestriol can significantly reduce the incidence of UTIs [6]. Hence, in these women, antimicrobial prophylaxis is only recommended if UTIs recur despite oestriol substitution. In premenopausal women, other methods can be used, including immunostimulation (eg, Uro-Vaxom®, Strovac®), probiotic therapy [9], urine acidification [10], and cranberry juice [11,12]. Until now, for most of these strategies, only a limited number of meaningful efficacy studies are available. Moreover, no studies that directly compare the efficacy of these alternative methods with antimicrobial prophylaxis have been performed. Therefore, more research on these strategies is urgently needed, since any improvement on prophylaxis will have a huge impact on health care and health economics.

3.2. Oral immunostimulant bacterial extracts: mechanism of action

The main goal of most alternative prophylactic strategies is not destroying and eliminating the infective agents, as for antimicrobial therapies, but protecting the host from infection. One way to do this is to prime the patient's mucosal immune system to react promptly against harmful *E. coli* by oral administration of the immunostimulant. The proof of concept for this strategy was first provided about 40 yr ago. Bacterial extracts were used empirically in immunocompetent patients to prevent recurrent infections. However, these attempts were hampered by a lack of knowledge of the exact mechanism of action. In 1987, the bacterial extract Uro-Vaxom (OM-89) was registered in Switzerland and Germany for the prophylaxis of recurrent cystitis. This preparation contains 6 mg lyophilised bacterial lysates derived from 18 *E. coli* strains that are most frequently responsible for UTIs. Since then, our understanding of the immune system has grown considerably, leading to a more solid rationale for the mechanism of action of immunostimulant bacterial extracts.

Nowadays, immunostimulating agents are known to exert their prophylactic effect by activating both the innate and the adaptive immune system, thereby enhancing the patient's natural defence. After ingestion, the components of the bacterial extract Uro-Vaxom can pass the stomach. Indeed, the antigenic bacterial proteins and peptides containing D-amino acids have been chemically modified to make them resistant to digestive proteases, while agonists and antagonists of the toll-like receptors TLR4 and TLR2, present in the extract, are amphiphilic molecules. Consequently, these components are absorbed in the ileum and jejunum. When bacterial fractions are recognised as "danger signals", mainly by the TLR4 [13], innate immunity is polarised. As a result, antigen-presenting cells in the Peyer's patches are stimulated: Maturation of dendritic cells is increased [14], phagocytotic activity of macrophages/neutrophiles is enhanced [15], expression of adhesion molecules at the neutrophile surface is elevated [16], and tumour necrosis factor α (TNF-α) and interleukin-12 (IL-12)

production by macrophages is induced [17]. Moreover, interferon-γ (IFN-γ) production by T cells is increased [18]. Activated T helper cells in turn stimulate the proliferation and activity of T and B lymphocytes [14,18,19]. Thus, the adaptive immune system is involved, as well. The stimulated B and T lymphocytes then migrate to mucosal-associated lymphoid tissues (MALTs), including the MALT of the urinary tract. There, they provide local immunoprotection by secreting immunoglobulin (Ig) A (IgA) molecules specific to the ingested bacterial fragments.

This proposed mechanism of action was supported by several animal experiments. In mice, repeated administration of Uro-Vaxom led to increased levels of IgG and IgA specific to all 18 *E. coli* strains in the extract. Ig levels were not only elevated in the serum of the mice [19] but also in lymphoid tissue of their urogenital tract [18]. In addition, the mice sera recognised several pathogenic (gram-positive as well as gram-negative) bacterial strains collected from patients with UTIs or with enterohemorrhagic *E. coli* infections that were different from the strains in the raw Uro-Vaxom extract [19]. Furthermore, in a mouse model of cystitis, oral administration of 1 mg Uro-Vaxom for 10 d caused a significant increase in bladder IFN-γ and IL-6 levels [20]. Importantly, the symptoms of bladder inflammation, being oedema, leukocyte infiltration, and haemorrhages, were also dramatically reduced. Thus, in animal experiments, the anti-inflammatory effect of oral immunostimulant bacterial extracts against *E. coli* infection was convincingly demonstrated.

3.3. Oral immunostimulant bacterial extracts: efficacy and tolerability

The efficacy of oral immunostimulation with *E. coli* extracts for the prophylaxis of recurrent UTIs was tested in five placebo-controlled, double-blind studies in nonimmunocompromised adult patients (Table 1). In four trials, patients taking one Uro-Vaxom capsule per day for 90 d experienced considerably less recurrent UTIs than patients taking placebo.

The number of enrolled patients and the follow-up period (12 mo) were the largest in the Prevention of Infection Recurrence by *E. coli* fractions in the Urinary tract System (PIREUS) study [21]. Adult women with at least three recurrent UTIs in the previous year were eligible for this study. They received one Uro-Vaxom capsule per day for 3 mo followed by 3 mo without treatment and a boost of one capsule per day for 10 d in months 7, 8, and 9. The number of patients without recurrences during the 12-mo follow-up period was significantly lower in the Uro-Vaxom–treated group than in the placebo-treated group

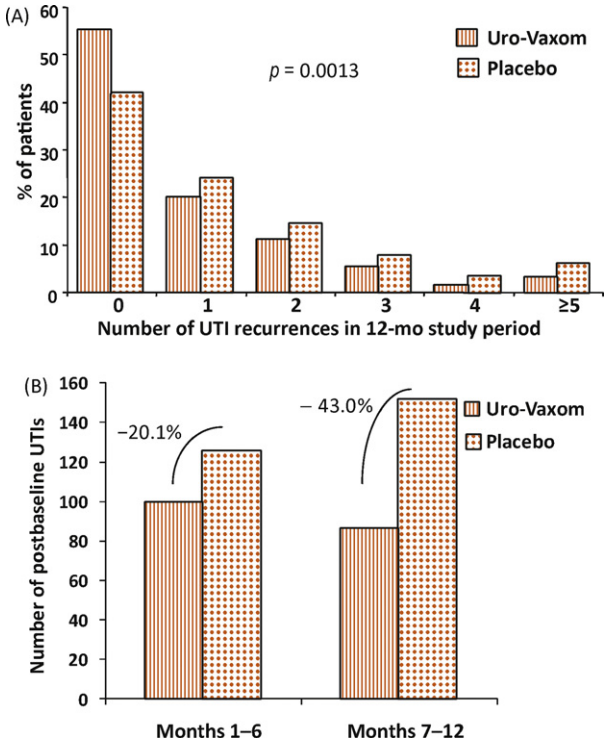

Fig. 3 – Uro-Vaxom more effectively prevents recurrence of urinary tract infections than placebo. Data are retrieved from a multinational, double-blind, placebo-controlled study in 454 women with recurrent urinary tract infections [21]. Number of postbaseline urinary tract infections was compared between patients receiving Uro-Vaxom (*n* = 231) and patients receiving placebo (*n* = 222). (A) Distribution of postbaseline urinary tract infections per patient. (*p*: 2-sided Mann-Whitney test). (B) Number of postbaseline urinary tract infections in months 1–6 and months 7–12. The percentage reduction in the Uro-Vaxom group versus the placebo group is also depicted.
UTI = urinary tract infection.

Table 1 – Overview of placebo-controlled, double-blind Uro-Vaxom studies

Author (yr)	No. of patients (UV/placebo)		Treatment scheme	Comparator	Parameters measured	Reduction in mean no. of recurrent UTIs with UV (expressed as % of placebo) [27]
	Admitted	Completed				
Tammen (1990) [28]	76/74	61/59	1/d for 90 d	Placebo	UTI, B, Ab, D	−34.9%
Pisani et al (1992) [29]	81/79	66/71	1/d for 90 d	Placebo	UTI, B, S, Ab, L	−43.9%
Schulman et al (1993) [30]	85/81	72/68	1/d for 90 d	Placebo	UTI, B, Ab, D	−37.8%
Magasi et al (1994) [31]	63/59	58/54	1/d for 90 d	Placebo	UTI, B, L, D	−65.2%
Bauer et al (2005) [21]	231/222	195/191 (184/186)*	1/d for 90 d; break 3 mo; then 10 d/mo for 3 mo; total 12 mo	Placebo	UTI, B, S, Ab, L, D	−21.7% (−34.4%)*

UV = Uro-Vaxom; UTI = urinary tract infection; B = bacteriuria; Ab = use of antibacterials; D = dysuria; S = symptoms; L = leukocyturia.
*12-mo follow-up.

(Fig. 3A). Conversely, the number of patients with many recurrences was higher in the placebo-treated group than in the Uro-Vaxom–treated group. Moreover, patients receiving the immunostimulant experienced fewer UTI symptoms (dysuria, pollakiuria, burning pain) in the 12-mo follow-up period than patients receiving placebo, and the total duration of the UTIs was shorter. Moreover, antibiotic use was considerably reduced following Uro-Vaxom prophylaxis (quinolones: −67%; β-lactams: −26.4%). Importantly, the preventive effect of immunostimulation for recurrent UTIs was mainly visible after the boost, that is, during the last 6 mo of follow-up (Fig. 3B).

The tolerability of Uro-Vaxom was tested in the previous clinical trials, as well. Only a few adverse events were reported. Thus, the agent is well tolerated. This good side-effect profile was also confirmed by close pharmacovigilance monitoring: During the past 5 yr, around 8 million patients were treated with Uro-Vaxom but only three serious adverse events were reported. Most of these events were gastrointestinal disorders. Most likely, they were caused by propylgallate or glutamate, which were constituents of the Uro-Vaxom capsule in the past. Therefore, the formulation of this excipient has been adapted recently.

In two clinical studies, the efficacy and safety of Uro-Vaxom for the prevention of recurrent UTIs was tested in specific subgroups, that is, in spinal cord injury patients and in pregnant women. In a 6-mo, double-blind cross-over study in 70 paraplegic patients, the UTI recurrence rate was significantly decreased in Uro-Vaxom–treated patients compared with placebo [22]. In an open-label, multicentre pilot study, 62 women in weeks 16–28 of pregnancy with recurrent UTIs received one capsule of Uro-Vaxom per day until delivery [23]. Only 19.4% of women experienced a UTI during the study versus 52.5% of women during the 6 mo prior to the study. Thus, the incidence of UTIs was significantly reduced during Uro-Vaxom prophylaxis ($p = 0.0002$). In addition, dysuria was markedly improved, and the need for antibiotic therapy was significantly decreased. Moreover, slight adverse events were only observed in two patients (nausea and heartburn), and all newborns were healthy, with normal Apgar scores. Hence, in this preliminary study, immunostimulation with *E. coli* fractions was well tolerated by the mother and by the foetus.

3.4. Oral immunostimulant bacterial extracts: burning questions and current challenges

Although oral immunostimulation with *E. coli* fractions effectively prevents recurrent, uncomplicated cystitis and is well tolerated, it is not yet recommended as a first-line strategy for the prophylaxis of recurrent UTIs in the EAU guidelines [4]. The main reason for this is the lack of clinical studies that directly compare the efficacy of standard antimicrobial prophylaxis with immunostimulant prophylaxis. Indeed, only in an open-label pilot study in female children was the efficacy of long-term Uro-Vaxom treatment for the prevention of recurrent UTIs compared with nitrofurantoin therapy. Here, both strategies turned out to be equally effective [24].

In addition, several aspects of prophylaxis with bacterial immunostimulants have not yet been investigated. First, the long-term efficacy of this strategy is currently unknown, because only one study had a follow-up period >6 mo (Table 1) [21]. Patient monitoring for at least 1 yr is very important, because the UTI recurrence rate is known to fluctuate over time. Second, the optimal immunostimulant treatment scheme has to be explored in more detail, comparing the "classical" treatment scheme of one capsule of Uro-Vaxom per day for 3 mo with a booster regimen [21]. Third, only a few specific subpopulations have been tested so far. Thus, the test population for oral immunostimulation should be broadened in order to define specific subpopulations that could benefit more from its preventive effects, such as children or pregnant women with recurrent UTIs. In addition, it would be interesting to test the efficacy of immunostimulation in patients with indications distinct from recurrent cystitis, such as chronic prostatitis. Finally, measuring more host- and pathogen-related parameters before, during, and at the end of the treatment period will give us a better insight into the mechanism of action of immunostimulation. For instance, to find out what is changing in the immune status of the patient during treatment, the type and levels of secretory IgA in the urine and in other organs can be determined. In this way, more information on how to optimise treatment can also be gathered.

3.5. Oral immunostimulant bacterial extracts: future developments

From the previous discussion, is it clear that there are still several unanswered questions concerning oral immunostimulation with *E. coli* fractions. In addition, the formulation of Uro-Vaxom was adapted over the last few years: Propylgallate and glutamate excipients were replaced by mannitol, and the *E. coli* culture medium of animal (bovine) origin was replaced by medium of vegetal (soybean) origin because of bovine spongiform encephalopathy issues. Hence, two new double-blind, placebo-controlled, randomised clinical studies have recently been initiated: one concerning Uro-Vaxom therapy for recurrent UTIs and one concerning the use of Uro-Vaxom in chronic prostatitis.

A first study (UV-2007/01) is a multicentre phase 3 trial in female patients suffering from uncomplicated, recurrent UTIs. This trial aims at comparing the efficacy of immunostimulation with *E. coli* fractions for the prevention of recurrent UTIs with standard antimicrobial prophylaxis recommended in the EAU guidelines, which is nitrofurantoin treatment. At least 440 patients will be recruited from 50 sites in Germany, Austria, and Slovakia. Patients in the first 3 mo receive either Uro-Vaxom or placebo, followed by 3 mo without treatment. At month 6, patients receive either Uro-Vaxom 10 d per month for 3 mo or nitrofurantoin for 3 mo. The primary end point is the mean rate of UTI at 9 mo, the end of the treatment period. As secondary end points, the incidence of acute, uncomplicated UTIs between months 7 and 12, the

severity of symptoms, and the type and duration of prescribed concomitant treatments will be assessed. Moreover, the follow-up period will be extended to 24 mo, and urinary secretory IgA and IgM levels will be measured.

In a second placebo-controlled phase 3 study (UV-2005/01), the efficacy and safety of Uro-Vaxom will be tested in 200 patients with chronic prostatitis (NIH type II and III)/chronic pelvic pain syndrome (CP/CPPS). The treatment regimen will be the same as in the UV-2007/01 study. The primary end point is the number of responders, that is, the number of patients with a reduction in National Institutes of Health Chronic Prostatitis Symptom Index score $\geq$6. The rationale for this study is the suggested role of autoimmune disorders and cytokines in the aetiology of CP/CPPS [25,26]. If CP/CPPS indeed has an autoimmune basis, immunologic approaches, such as oral administration of immunostimulant bacterial extracts, will most likely turn out to be effective treatment options.

4. Conclusions

Currently, oral administration of immunostimulant *E. coli* fractions is classified in the EAU guidelines as an alternative method for the prevention of recurrent UTIs, while antibiotic prophylaxis is still considered the first-line strategy. However, more and more scientific data have become available from in vitro and animal studies that support the concept of immunostimulation. Moreover, the efficacy and tolerability of this strategy was repeatedly demonstrated in several clinical studies. New clinical trials have now been set up to compare the long-term efficacy of Uro-Vaxom with standard antimicrobial prophylaxis, to determine its optimal dose and treatment regimen, and to test its efficacy in new indications such as chronic prostatitis. In addition, patient parameters such as secretory IgA and cytokines will be measured during and at the end of the studies to give us a better insight into the mechanism of action of this therapeutic agent. Together, these new studies should provide convincing evidence that immunostimulation with *E. coli* fractions can be used as a first-line strategy for the prophylaxis of recurrent UTIs.

Conflicts of interest

Kurt G. Naber is an investigator and consultant for OM PHARMA. Gabriel Cozma is the head of the Medical and Regulatory Affairs Department of OM PHARMA.

Funding support

None.

Acknowledgments

The authors are grateful to Ismar Healthcare NV for assistance in the writing of this manuscript.

References

[1] Foxman B. Epidemiology of urinary tract infections: incidence, morbidity, and economic costs. Am J Med 2002;113(Suppl 1A): 5S–13S.

[2] Naber KG, Schito G, Botto H, Palou J, Mazzei T. Surveillance study in Europe and Brazil on clinical aspects and antimicrobial resistance epidemiology in females with cystitis (ARESC): implications for empiric therapy. Eur Urol 2008;54:1164–78.

[3] Wagenlehner FM, Weidner W, Naber KG. Emerging drugs for bacterial urinary tract infections. Expert Opin Emerg Drugs 2005;10:275–98.

[4] Grabe M, Bishop MC, Bjerklund-Johansen TE, et al. Guidelines on urological infections. European Association of Urology Web site. http://www.uroweb.org/professional-resources/guidelines/online/ . Updated 2009. Accessed May 2009.

[5] Hooton TM, Scholes D, Hughes JP, et al. A prospective study of risk factors for symptomatic urinary tract infection in young women. N Engl J Med 1996;335:468–74.

[6] Raz R, Stamm WE. A controlled trial of intravaginal estriol in postmenopausal women with recurrent urinary tract infections. N Engl J Med 1993;329:753–6.

[7] Raz R, Chazan B, Kennes Y, et al. Empiric use of trimethoprim-sulfamethoxazole (TMP-SMX) in the treatment of women with uncomplicated urinary tract infections, in a geographical area with a high prevalence of TMP-SMX-resistant uropathogens. Clin Infect Dis 2002;34:1165–9.

[8] Albert X, Huertas I, Pereiró II, Sanfélix J, Gosalbes V, Perrota C. Antibiotics for preventing recurrent urinary tract infection in non-pregnant women. Cochrane Database Syst Rev 2004:CD001209.

[9] Reid G. Probiotic therapy and functional foods for prevention of urinary tract infections: state of the art and science. Curr Infect Dis Rep 2000;2:518–22.

[10] Fünfstück R, Straube E, Schildbach O, Tietz U. Prevention of reinfection by L-methionine in patients with recurrent urinary tract infection. Med Klin (Munich) 1997;92:574–81.

[11] Avorn J, Monane M, Gurwitz JH, Glynn RJ, Choodnovskiy I, Lipsitz LA. Reduction of bacteriuria and pyuria after ingestion of cranberry juice. JAMA 1994;271:751–4.

[12] Jepson RG, Mihaljevic L, Craig J. Cranberries for preventing urinary tract infections. Cochrane Database Syst Rev 2004:CD001321.

[13] Bessler WG, Puce K, vor dem Esche U, Kirschning C, Huber M. Immunomodulating effects of OM-89, a bacterial extract from *Escherichia coli,* in murine and human leukocytes. Arzneimittelforschung/Drug Research. In press.

[14] Schmidhammer S, Ramoner R, Höltl L, Bartsch G, Thurnher M, Zelle-Rieser C. An *Escherichia coli*-based oral vaccine against urinary tract infections potently activates human dendritic cells. Urology 2002;60:521–6.

[15] Van Pham T, Kreis B, Corradin-Betz S, Bauer J, Mauël J. Metabolic and functional stimulation of lymphocytes and macrophages by an *Escherichia coli* extract (OM-89): in vitro studies. J Biol Response Mod 1990;9:231–40.

[16] Marchant A, Duchow J, Goldman M. Adhesion molecules in antibacterial defenses: effects of bacterial extracts. Respiration 1992;59(Suppl 3):24–7.

[17] Chiavaroli C, Moore A. An hypothesis to link the opposing immunological effects induced by the bacterial lysate OM-89 in urinary tract infection and rheumatoid arthritis. BioDrugs 2006;20:141–9.

[18] Huber M, Krauter K, Winkelmann G, et al. Immunostimulation by bacterial components: II. Efficacy studies and meta-analysis of the bacterial extract OM-89. Int J Immunopharmacol 2000;22: 1103–11.

[19] Huber M, Baier W, Serr A, Bessler WG. Immunogenicity of an *E. coli* extract after oral or intraperitoneal administration: induction of

antibodies against pathogenic bacterial strains. Int J Immunopharmacol 2000;22:57–68.

[20] Lee SJ, Kim SW, Cho YH, Yoon MS. Anti-inflammatory effect of an *Escherichia coli* extract in a mouse model of lipopolysaccharide-induced cystitis. World J Urol 2006;24:33–8.

[21] Bauer HW, Alloussi S, Egger G, Blümlein H-M, Cozma G, Schulman CC, on behalf of Multicenter UTI Study Group. A long-term, multicenter, double-blind study of an *Escherichia coli* extract (OM-89) in female patients with recurrent urinary tract infections. Eur Urol 2005;47:542–8.

[22] Hachen HJ. Oral immunotherapy in paraplegic patients with chronic urinary tract infections: a double-blind, placebo-controlled trial. J Urol 1990;143:759–62.

[23] Baertschi R, Balmer JA, Eduah SB, Liechti A, Lurie D, Schams H. Bacterial extract for the prevention of recurrent urinary tract infections in pregnant women: a pilot study. Int J Immunother 2003;19:25–31.

[24] Lettgen B. Prevention of recurrent urinary tract infections in female children: OM-89 immunotherapy compared with nitrofurantoin prophylaxis in a randomized pilot study. Curr Ther Res 1996;57: 464–75.

[25] Rudick CN, Schaeffer AJ, Thumbikat P. Experimental autoimmune prostatitis induces chronic pelvic pain. Am J Physiol Regul Integr Comp Physiol 2008;294:R1268–75.

[26] Desireddi NV, Campbell PL, Stern JA, et al. Monocyte chemoattractant protein-1 and macrophage inflammatory protein-1alpha as possible biomarkers for the chronic pelvic pain syndrome. J Urol 2008;179:1857–61.

[27] Naber KG, Cho YH, Matsumoto T, Schaeffer AJ. Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. Int J Antimicrob Agents 2009;33:111–9.

[28] Tammen H. Immunobiotherapy with Uro-Vaxom in recurrent urinary tract infection. The German Urinary Tract Infection Study Group. Br J Urol 1990;65:6–9.

[29] Pisani E, Palla R, Bono AV. Double-blind randomised clinical study of OM-8930 vs placebo in patients suffering from recurrent urinary tract infections [quoted by Chiavaroli C, Moore A. An hypothesis to link the opposing immunological effects induced by the bacterial lysate OM-89 in urinary tract infection and rheumatoid arthritis. BioDrugs 2006; 20:141–9]. Geneva, Switzerland: OM PHARMA; 1992.

[30] Schulman CC, Corbusier A, Michiels H, Taenzer HJ. Oral immunotherapy of recurrent urinary tract infections: a double-blind placebo-controlled multicenter study. J Urol 1993;150: 917–21.

[31] Magasi P, Pánovics J, Illés A, Nagy M. Uro-Vaxom and the management of recurrent urinary tract infection in adults: a randomized multicenter double-blind trial. Eur Urol 1994;26:137–40.