Recurrent Uncomplicated Urinary Tract Infections – The Place of Immuno-prophylaxis

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Abstract

Recurrent uncomplicated urinary tract infections (UTIs), especially cystitis in women, are very common and impose a substantial disease burden in populations worldwide. While acute episodes can be successfully treated with antibiotics, they often fail to prevent recurrence; pathogenic bacteria re-establish and symptoms reappear within a few months. The intractable nature of some UTIs and the alarming development of antibiotic resistance have stimulated efforts to identify non-antibiotic and more effective treatments that provide a better solution. Such alternatives are diverse and include probiotics, cranberry juice and hormonal therapies, but these have shown limited efficacy. Another approach, immuno-active prophylaxis with Uro-Vaxom®, has been more widely studied and its use is supported by an extensive body of clinical evidence. In this treatment, patients receive oral capsules containing an extract from multiple pathogenic *Escherichia coli* strains (Uro-Vaxom). Mechanism of action studies show that Uro-Vaxom effectively stimulates both innate and adaptive immune responses against UTI pathogens. In a series of large clinical trials and in regular clinical use, Uro-Vaxom has proven to be a highly effective and well-tolerated approach to treating recurrent UTIs. In a larger example of these trials, Uro-Vaxom reduced the frequency of UTI recurrences by 34%, the duration of recurrences by 49% and significantly reduced the consumption of antibiotics compared with placebo. These positive results led the European Association of Urology guidelines to recommend its use for prevention of recurrent UTI.

Keywords

Recurrent urinary tract infection, immunoprophylaxis, immunostimulant treatment, guidelines, clinical evidence, mode of action

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The Guidelines Offer More than One Option to Prevent Recurrent Urinary Tract Infections

Despite the availability of antibiotics and improved hygiene practices, recurrent urinary tract infections (rUTIs) remain common and a significant cause of morbidity in populations throughout the world. These are believed to be the most common human bacterial infection and affect various groups including young children, the elderly, patients with spinal cord injuries, multiple sclerosis or with catheters, but are most common among otherwise healthy adult women. In sexually active women, intercourse is the trigger for 75–90 % of UTIs.[1–3] Nearly one in three women has had a UTI by the age of 24,[4] almost half of them will subsequently experience another episode and 20–30 % will have rUTIs, defined as at least two acute episodes per six months or at least three per year. In the US, UTIs account for almost seven million doctor's office visits and 100,000 hospitalisations per year,[5] and consequently expend considerable medical resources.

Various bacterial species cause UTIs but the majority are caused by pathogenic strains of *Escherichia coli*. This was emphasised by the Antimicrobial Resistance Epidemiological Survey in Cystitis (ARESC) study, which included 4,264 patients at 68 European and Brazilian treatment centres. The results showed that 76.7 % of UTIs were caused by *E. coli*, the remainder being caused by various Gram-negative species such as *Klebsiella pneumoniae, Enterobacter faecalis* and *Proteus mirabilis* and some Gram-positive bacterial species such as *Staphylococcus saprophyticus* (see *Figure 1*).[6] Similar proportions of bacterial pathogens have been shown in other studies on cystitis.[7–9]

In uncomplicated acute cystitis, short-term antibiotic therapy can provide rapid resolution of symptoms with good safety and tolerability and low cost with a generally low impact on host flora. However, the number of suitable antibiotics is limited due to growing problems of bacterial resistance, compliance and adverse events. In the ARESC study, pathogenic *E. coli* strains isolated from female patients with uncomplicated cystitis were >90 % susceptible to fosfomycin, mecillinam, and nitrofuratoin in all countries, with varying susceptibility to ciprofloxacin between 86 and 98 % depending on the country, and with susceptibility to cotrimoxazole and ampicillin <80 % across Europe and Brazil (see *Table 1*).[6]

Table 1: Antimicrobial Susceptibility Patterns for *Escherichia coli* by Country in the Antimicrobial Resistance Epidemiological Survey in Cystitis (ARESC) Study

Antibiotic	Country (Number of Bacterial Isolates) % *Escherichia coli* Strains Susceptible									
	Spain (515)	France (409)	Germany (243)	Russia (301)	Italy (239)	Brazil (374)	Poland (90)	Austria (62)	The Netherlands (29)	Hungary (52)
Fosfomycin	97.2	99.0	97.9	99.3	97.9	97.0	98.8	100	100	100
Mecillinam	94.1	97.0	97.5	97.3	94.1	94.6	97.7	100	96.5	96.1
Nitrofurantoin	94.1	97.3	92.5	94.7	97.4	94.3	92.2	100	100	98.0
Ciprofloxacin	89.3	98.2	96.3	86.4	87.9	89.2	93.3	98.3	96.5	96.2
Nalidixic acid	73.5	93.6	90.5	82.7	73.6	75.4	84.4	91.9	93.1	67.3
Amoxicillin/ clavulanic acid	80.9	90.9	88.8	83.1	71.5	79.8	86.6	93.5	82.8	51.9
Cefuroxime	79.0	89.2	93.0	85.7	77.8	74.5	81.1	77.4	89.6	73.0
TMP-SMX	66.2	87.7	74.0	69.4	71.1	54.4	80.0	70.9	79.3	59.6
Ampicillin	35.3	60.8	59.2	42.0	43.0	37.7	40.0	43.5	65.5	32.6

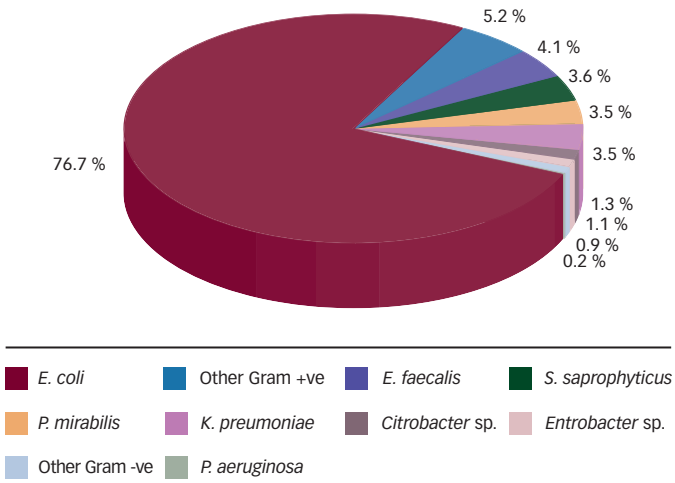
Green = urinary tract infection (UTI) strains mostly susceptible (<10% resistant); amber = UTI strains show some resistance (≥10 % resistant); red = UTI strains show widespread resistance (>20 % resistant). Susceptibility levels: fosfomycin ≤64 mg/l; mecillinam ≤8mg/l; nitrofurantoin ≤32 mg/l; ciprofloxacin ≤1 mg/l; amoxi/clav ≤8/4 mg/l; naladixic acid ≤16 mg/l; cefuroxime ≤4 mg/l; trimethoprim and sulphamethoxazole (TMP-SMX) ≤2/38 mg/l; ampicillin ≤8 mg/l. Source: Naber et al., 2008.[6]

The limitations of antibiotic therapy in UTIs were highlighted in a study in Israel on 544 bacterial cultures from 618 women with lower UTI and/or pyuria/bacteriuria.[10] Bacterial cultures isolated were mainly *E. coli* and 71 % were susceptible to trimethoprim with sulphamethoxazole (TMP-SMX) but 29 % were resistant. Five to nine days after a five-day course of treatment, patients with susceptible strains had an 88 % clinical cure rate compared with 54 % in those with resistant strains. The authors considered this an unacceptable failure rate and suggested that TMP-SMX should not be used in UTIs in areas of high resistance. They also noted that TMP-SMX-resistant strains are likely to be resistant to multiple other antibiotics and recommended fluoroquinolones or nitrofurantoin as alternatives. Nevertheless, in patients with recurrent UTI, simply treating acute episodes of cystitis is insufficient; the likelihood of recurrences has to be considered as acute antibiotic treatments do not prevent recurrence.[1]

Susceptibility to recurrent UTIs is increased by clinical factors including a history of UTI, urinary problems and abnormalities, diabetes mellitus, behavioural factors including sexual intercourse, spermicide, diaphragm or recent antibiotic use and other factors including oestrogen deficiency, urological surgery and detrusor dyssynergy.[1] Recurrent UTIs require careful management; if the recurrences become frequent, antibiotic prophylaxis should be considered.[11,12] The current antimicrobial options for prophylaxis are daily/weekly or post-coital low doses of antimicrobials or short-term therapy.

Recommended antibiotic regimens used in UTI prophylaxis are nitrofurantoin (50–100 mg/day), trimethoprim (50–100 mg/day), TMP-SMZ (40–200 mg/day or three doses/week) or fosfomycin trometamol (3 g/10 days). In pregnant women cephalexin 125–500 mg/day is recommended.[11] However, the Agence Française de Sécurité Sanitaire des Produits de Santé (AFSSAPS) recently advised that due to hepatic and pulmonary adverse events, nitrofurantoin should not be used for prophylaxis and patients receiving this drug must be monitored and made aware of possible side effects.[13] The European Association of Urology (EAU) guidelines state that antimicrobial prophylaxis to prevent rUTIs should be considered only after counselling and attempted behavioural modification (grade of recommendation [GoR]: A) and that continuing antimicrobial prophylaxis should be considered to prevent recurrent uncomplicated cystitis only in women in whom non-antimicrobial measures have been unsuccessful (GoR A).[11,12]

Figure 1: Bacterial Aetiology (Species and Percentage) of Uncomplicated Urinary Tract Infection in the Antimicrobial Resistance Epidemiological Survey in Cystitis (ARESC) Study



Numbers are percentages of strains isolated from urinary tract infection patient samples.

One such non-antimicrobial measure is to use probiotics in which capsules containing suspensions of non-pathogenic benign bacterial species such as *Lactobacillus, Bifidobacteria* or *Saccharomyces* are applied to the vagina to colonise and displace pathogenic species.[14–16] An example of such therapy was investigated in a recent trial in which 48 women with a history of UTI at a medical centre in Seattle received intravaginal *Lactobacillus crispatus* (Lactin-V) over 10 weeks. This treatment significantly reduced UTI episodes compared with another group receiving placebo ($p<0.01$).[17] This probiotic approach has shown some efficacy and safety in several other small trials but much larger randomised studies are required. The EAU guidelines state that regular intravaginal use of the probiotic containing lactobacilli could be recommended for prophylaxis of rUTI (GoR C).[16]

Another non-antimicrobial approach to rUTIs is bacterial interference in which bacteria of low virulence are used to induce bacteriuria in order to colonise urinary sites and inhibit symptomatic infection by pathogenic strains. Some limited clinical data also support this concept.[18] An alternative treatment in post-menopausal women is

Table 2: Major Clinical Studies in the Development of Uro-Vaxom

Author/Date	Study Duration	Patients (with rUTI)	Design	*Dose and Follow-up	Main Results
Frey et al., 1986[44]	6 months	64 adult males and females	Randomised, double blind, placebo controlled	1 capsule** daily for 3 months or placebo + 3 months follow-up	Reduction in the incidence of bacteriuria, leukocyturia and dysuria at 6 months ($p<0.05$) Reduction in the duration of concomitant antibiotic use ($p<0.01$)
Tammen 1990[45]	6 months	120 adult males and females	Randomised, double blind, placebo controlled	1 capsule/daily for 3 months or placebo + 3 months follow-up	Reduction in the mean number of recurrences ($p<0.001$) 38 % with no recurrences versus 17 % for the placebo ($p<0.001$)
Schulman et al., 1993[28]	6 months	166 adult males and females	Randomised, multicentre, double blind, placebo controlled	1 capsule daily for 3 months or placebo + 3 months follow-up	49 % reduction in the number of recurrences at 6 months ($p<0.0001$) 66 % reduction in the number of antibiotic treatment days ($p<0.002$)
Magasi et al., 1994[27]	6 months	112 adult males and females	Randomised, multicentre, double blind, placebo controlled	1 capsule daily for 3 months or placebo + 3 months follow-up	67 % with no recurrences versus 22 % for the placebo ($p<0.0005$) Reduction in the incidence of bacteriuria ($p<0.001$), leukocyturia and dysuria at 6 months ($p<0.005$)
Bauer et al., 2005[26]	12 months	453 adult females	Randomised multicentre double blind, placebo controlled	1 capsule daily 3 months or placebo + 3 months no treatment + booster series of 1 capsule daily for first 10 days of months 7, 8 and 9 + follow up to month 12.	34 % reduction in the number of recurrences at 12 months ($p<0.003$) Reduction in the mean number of anti-infective prescriptions ($p=0.005$)

**Patients were given concomitant antibiotics as necessary; **One capsule = 6mg. rUTI = recurrent urinary tract infection*

local oestrogen substitution. Topical oestriol treatment can significantly reduce UTI incidence, increase numbers of UTI-free patients and increase vaginal lactobacilli, indicative of a more benign bacterial flora.[19]

A popular treatment for rUTIs is cranberry or lingonberry juice or extract resulting in urine acidification. However, a Cochrane analysis[20] identified only one study reporting significant results for reducing symptomatic UTIs and noted that adverse events and drop-outs were common. Cranberry juice shows some evidence of decreasing UTIs in women but larger trials are needed;[21] however, a number of trials have shown negative results.[22] The EAU guidelines state that daily consumption of cranberry products could be recommended for prophylaxis of rUTI (GoR C).[11,23]

The most successful and most-developed non-antimicrobial measure is immunoactive prophylaxis in which antigens from pathogenic bacteria are administered orally or locally and stimulate an improved immune response at infected sites, such as the urinary tract. In a meta-analysis of 11 blind, controlled trials (seven with an oral *E. coli* extract, OM-89 [Uro-Vaxom®], four with vaginal vaccine), Uro-Vaxom showed substantial reductions in UTI.[24] These positive results led to an EAU recommendation that Uro-Vaxom should be used for immunoprophylaxis in female patients with rUTI (GoR B, Level 1A).[11]

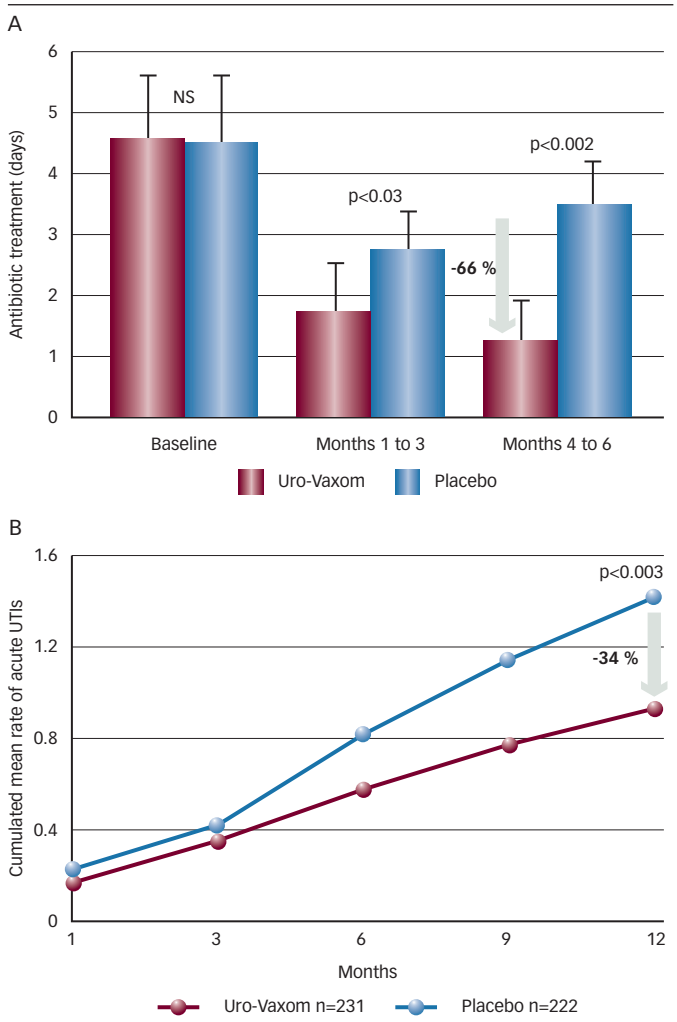
Clinical Evidence of Uro-Vaxom in the Management of Recurrent Lower Urinary Tract Infections

Uro-Vaxom is currently the only non-antimimicrobial prophylactic regimen recommended with grade B as immunoactive prophylaxis by the EAU guidelines. It is prepared from the lysates of 18 pathogenic *E.coli* strains and formulated as a 6 mg oral capsule.[25] Clinical development of Uro-Vaxom has involved trials including >2,000 patients with rUTIs and in clinical use over one million patients have been treated over a five-year period.[24] Uro-Vaxom can be initiated concomitantly with antibiotics at the onset of an acute episode in order to prevent further infections.

The major randomised placebo-controlled clinical trials on patients with rUTIs have all shown substantial benefits from Uro-Vaxom treatment (see *Table 2*) and all have shown significant reductions in recurrences over six months or one year compared with placebo ($p<0.003$ to <0.0001).[26–28] In one study on 160 adults with rUTIs in Belgium (84 % female with at least two recurrences/year), patients were randomised to one capsule of Uro-Vaxom/day (n=82) or placebo (n=78) for three months, followed by a three-month observation period.[28] Compared with placebo, during treatment and follow-up, Uro-Vaxom reduced the numbers of recurrences by 48 and 51 %, respectively. During these study periods, Uro-Vaxom also substantially reduced the number of days patients received antibiotics (by 35 and 66 %, respectively) compared with placebo (see *Figure 2A*). In addition, Uro-Vaxom significantly reduced bacteriuria, leukocyturia, erythrocyturia, nitrituria, albuminuria and casts in urine and was generally safe and well tolerated; the incidence of adverse events was greater with placebo than with active treatment (6 versus 2 %, respectively).

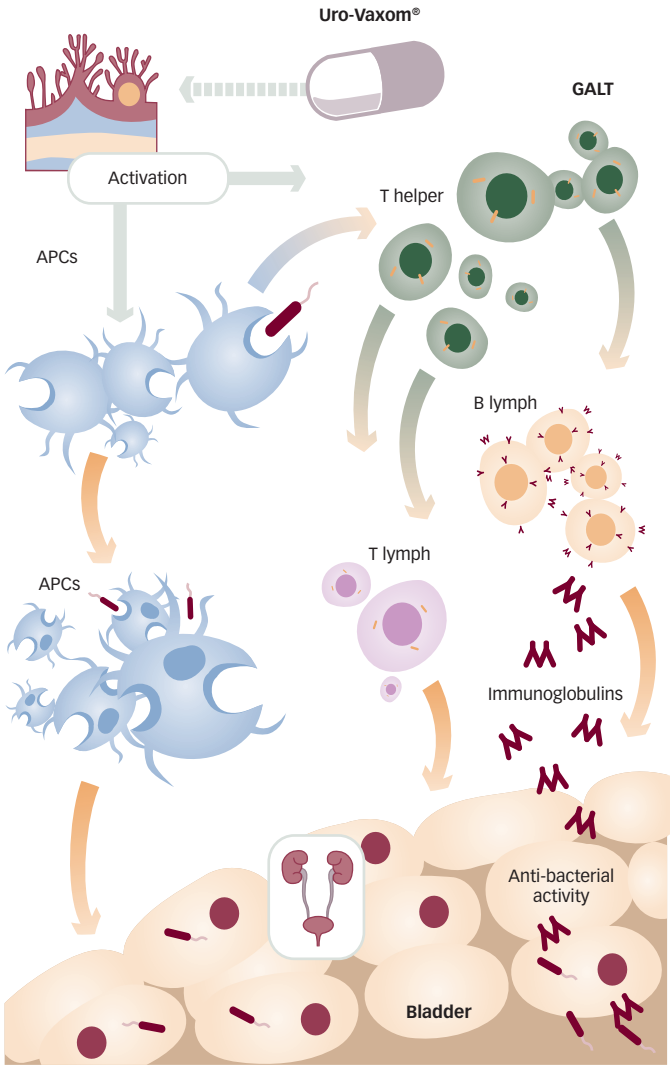
In a similar randomised, multicentre study conducted in Hungary, 112 patients (85 % female) with recurrent lower UTIs ($\geq 10^5$ bacteria/ml in midstream urine) were treated, either with one capsule Uro-Vaxom/day) for three months, or placebo, followed by a three-month follow-up period.[27] Amongst the Uro-Vaxom-treated group, 67.2 % were free of any recurrence compared with 22.2 % in the placebo group ($p<0.0005$).

Figure 2: Number of Days Receiving Antibiotic Treatment (A) and Cumulated Mean Rate of Acute Urinary Tract Infections (B) in Adult Patients with Recurrent Urinary Tract Infection During Treatment with Uro-Vaxom or Placebo



Negative percentage shows reduction in antibiotic treatment days in A and reduction in UTI recurrence during months 1–6 in B. In graph A, p-values were derived using Kruskall-Wallis test. UTIs = urinary tract infections. In graph B, p-values were derived using the Chi-square test. Sources: Bauer et al., 2005,[26] Schulman et al., 1993.[28]

Figure 3: Putative Mode of Action of Uro-Vaxom in Stimulating an Increased Immune Response to Bacterial Infection in Recurrent Urinary Tract Infection



APCs = antigen-presenting cells; B lymph = B lymphocytes; GALT = gut-associated lymphoid tissue; T lymph = T lymphocytes.

Bacteriuria, dysuria and leukocyturia were also significantly reduced (p<0.001 to <0.005 after six months) and no side effects were recorded in patients receiving Uro-Vaxom.

A more recent and larger multicentre study conducted in 11 countries in Europe explored the advantages of adding a booster dose of Uro-Vaxom after initial treatment as used in earlier trials.[26] From a population of 453 female patients with rUTIs (at least three recurrences in the previous year and ≥10^3 bacteria/ml in urine), 231 were initially randomised to Uro-Vaxom and 222 to placebo for three months. After a three-month interval, the former group was further treated with one capsule of Uro-Vaxom per day for the first 10 days of months seven, eight and nine and then followed up for a further three months. Compared with placebo, during months one to six Uro-Vaxom reduced UTI incidence by 20 % but during months seven to twelve it was reduced by 43 %, showing an enhanced effect after boosting. Antibiotic prescriptions were significantly reduced by Uro-Vaxom (2.44 versus 2.79 per patient; p<0.005) and the incidence of dysuria, pollakisuria and burning pain decreased compared with placebo. The overall reduction in frequency of UTI recurrences was 34 % (see *Figure 2B*) and the total duration of recurrences was 49 % shorter with Uro-Vaxom compared with placebo. Adverse events, mainly headache and gastrointestinal symptoms, occurred at similar frequencies in both groups and serious events were not attributed to the treatment.

In all of the clinical trials Uro-Vaxom was shown to be a highly effective approach to the therapeutic management of rUTIs. Treatment produced an improvement in all UTI symptoms compared with placebo. Recurrences were significantly reduced in each trial and this was substantially increased with booster treatment. In addition, the overall duration of UTI recurrences and the need for antibiotic therapy were significantly reduced. These efficacy findings, favourable safety profile and low incidence of any adverse events make Uro-Vaxom a suitable option to treat persistent infection in many patients with recurrent UTIs.

Uro-Vaxom – Molecular Basis Shaping the Immune Response

Adequate defence against bacterial infection in the urinary tract, as at other body sites, requires the full functioning of both the innate and

adaptive immune systems. In individuals in whom any part of these systems is compromised, due to genetic, medical or other factors, there is a greater risk of infections. Both innate and adaptive responses are important in the recognition of antigenic structures present on the surface of bacteria in UTIs and in initiating effective responses leading to isolation and destruction of the pathogen.[29] In many *in vitro* and *in vivo* investigations, and some human studies, the immunoactive properties of Uro-Vaxom have been extensively investigated and the data indicate that it stimulates both innate and adaptive immune responses. A general schematic of Uro-Vaxom action is given in *Figure 3*.

Innate Immune Pathways

Macrophages, dendritic cells and epithelial cells have different pattern recognition receptors (PRRs) such as toll-like receptors (TLRs) that are crucial to trigger innate immunity. These receptors recognise pathogenic components, including those contained in Uro-Vaxom, by a pattern recognition process and initiate responses that target and destroy pathogens.[30–32]

Genetic studies on large populations of women have shown that specific polymorphisms in their TLR genes confer protection against UTIs and pyelonephritis, while other polymorphisms increase risk of these and of asymptomatic bacteriuria.[33–35] Collectively, these results may indicate that some individuals are genetically predisposed to UTIs due to specific defects in their innate immune response.

In vitro studies performed by numerous investigators have shown that Uro-Vaxom stimulates the activity of macrophages and neutrophils,[25,36–38] increases maturation in dendritic cells[39] and increases the expression of adhesion molecules by neutrophils.[40] Furthermore, mouse model studies have shown that Uro-Vaxom increases leukocyte activity in blood and tumour necrosis factor alpha (TNF-α) secretion by peritoneal cells,[36] as well as immunoglobulin G (IgG) in spleen cell supernatants.[41] The molecular mechanism by which Uro-Vaxom stimulates innate immune cells is likely due to its capacity to activate pattern recognition receptors such as TLR2 and TLR4.[36]

Adaptive Immune Pathways

At the surface of the gut epithelium, bacteria or bacterial components (such as those in Uro-Vaxom) are recognised by dendritic cells and initiate multiple adaptive immune pathways. In one such pathway, activated dendritic cells interact with naïve T lymphocytes that differentiate and present the bacterial antigens to B cells in the Peyer's patches leading to secretion of immunoglobulins.[30] The resulting presence of IgA in the urinary epithelium is an important factor in the prevention of UTIs and recurrence.

In important animal model studies, mice were repeatedly treated with multiple Uro-Vaxom doses either orally or intraperitoneally.[42] Serum IgA and IgG levels against all 18 *E.coli* antigens were substantially raised compared with control mice for both methods of administration. This indicates a potential protective effect of Uro-Vaxom; stimulating IgAs that act as an antigen-specific barrier to pathogens in the urinary epithelium. The IgAs and IgGs secreted were also cross-reactive with other strains and species of bacterial pathogens isolated from UTIs. Uro-Vaxom may therefore provide protection against a greater number of UTI pathogens than those used in its formulation.

A substantial body of evidence now supports the immune-active nature of Uro-Vaxom in non-clinical settings. However, the demonstrated efficacy of Uro-Vaxom in treating UTIs raises questions in terms of its mode of action in humans and how oral administration of bacterial antigens can stimulate a stronger immune response to pathogens in the urinary epithelium to which the host has previously been exposed. The reason for this increased immunoactivity is likely to be a result of the molecular size of Uro-Vaxom components and structural changes that occur during the preparation process. In the gut, Uro-Vaxom constituents may penetrate the gut epithelium more effectively than whole bacteria, eliciting a stronger response and once absorbed, antigenic sites may be made conformationally more accessible.

A study in Poland on children with rUTIs showed that Uro-Vaxom treatment increased secretory IgA levels in urine for at least three months and during this time, protected 92 % of the patients from further UTIs.[43] This study is consistent with the *in vitro* and *in vivo* work described above, encouraging further investigations to more fully elucidate the immunostimulatory activity of Uro-Vaxom in humans.

Future Developments in Immunostimulant Treatment of Urological Infections

In the trials completed to date, the use of Uro-Vaxom in UTIs was compared only with placebo. To better assess its utility in practice, a clinical trial is currently investigating its efficacy versus a standard antimicrobial prophylaxis. In this trial, a recruitment of 446 patients with uncomplicated UTIs is planned, at 50 study centres in Germany, Austria and Slovakia. The patients are treated with Uro-Vaxom using the standard three-month regimen (versus placebo) followed by a three-month interval and then three months of the booster dosing regimen (versus nitrofurantoin treatment in the placebo group), and three months of follow-up. The results of this trial will provide urologists with a valid comparison between Uro-Vaxom immunoactive prophylaxis and standard antibiotic therapy to critically assess its potential as a means of preventing recurrent UTIs.

Another clinical trial is also in progress to evaluate the efficacy and safety of Uro-Vaxom in a different indication, the treatment of chronic prostatitis/chronic pelvic pain syndrome in a population of 200 male patients aged 30–60 years at 27 study centres in Europe. The primary end-point is the number of 'responder' patients showing a reduction in specified chronic prostatitis symptoms.

Conclusion

The efficacy of Uro-Vaxom in reducing the burden of recurrent UTIs in clinical trials and in office-based practice has demonstrated the validity of this immunoactive prophylaxis as a non-antimicrobial approach to preventing recurrent infections. This prophylaxis can be initiated concomitantly with antibiotics at the onset of a recurrent episode, in order to prevent further infections. The efficacy in clinical use, the antibiotic sparing advantage and favourable safety profile of Uro-Vaxom and its emerging potential for treating a wider range of urological infections is likely to increase interest amongst urologists. This is also likely to increase usage of this valuable immunoactive approach for managing recurrent UTIs and persistent urological infections as recommended in the guidelines. ■

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