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Functional Urology

First experience in the UK of treating women with recurrent urinary tract infections with the bacterial vaccine Uromune®

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Objectives

To determine the effectiveness of Uromune® in preventing recurrent urinary tract infections (UTIs) in women.

Patients and Methods

A total of 77 women with microbiology-proven recurrent UTIs were given Uromune sublingual vaccine for a period of 3 months. Time to first UTI recurrence since treatment and adverse events were prospectively recorded in a follow-up period of up to 12 months.

Results

Of the 77 women, 75 completed the treatment. Of the 75 women who completed treatment, 59 (78%) had no subsequent UTIs in the follow-up period. Prior to treatment, all women had experienced a minimum of three or more episodes of UTI during the preceding 12 months. Proportionally, the majority of recurrences occurred in postmenopausal women. One patient had to stop treatment because of an adverse event (rash over face and neck).

Conclusion

This prospective study suggests that Uromune is safe and effective at preventing UTIs in women. Further research is required in larger groups of patients for longer treatment times. An international double-blind randomized control trial comparing Uromune with placebo is currently underway.

Keywords

recurrent UTI, bacterial vaccine, immunomodulation

Introduction

Urinary tract infections are one of the most prevalent conditions worldwide, typically affecting a larger number of women than men. Recurrent UTIs are defined as three or more episodes of UTI during a 12-month period, or two or more episodes within 6 months. Up to 20–30% of women who previously experienced a UTI will develop recurrent UTIs [1].

Often these women rely on long-term antibiotic prophylaxis; however, with the alarming global rise in antibiotic resistance, there is a growing urgency to find alternative antibiotic-free treatment options. The problem is such that the WHO implemented a Global Action Plan in 2015 to tackle antimicrobial resistance [2]. The five strategic objectives of this plan are: (i) to improve awareness and understanding of antimicrobial resistance; (ii) to strengthen knowledge through surveillance and research; (iii) to reduce the incidence of infection; (iv) to optimize the use of antimicrobial agents; and (v) to develop the economic case for sustainable investment that takes account of the needs of all countries and increases investment in new medicines, diagnostic tools vaccines and other interventions.

With UTIs comprising a large proportion of infections worldwide that require the use of antibiotics, research into UTIs is rapidly growing. The current and new preventative measures in the treatment of UTIs have recently been reviewed [3]. One potential treatment option is an immunomodulation vaccine that utilises the patients' own immune system to prevent recurrent UTIs.

The genitourinary tract uses an innate and adaptive mucosal immune system to fight against uropathogens. This forms part of the mammalian lymphoid organ system, an immune system comprising 80% of all immunocytes and various different areas of the body. Immunocytes transit various mucosal associated lymphoid tissue (MALT) sites, therefore, dissemination of immunity to various MALT sites is possible via the activation of lymphocytes at one distant MALT site [4]. Various studies have found that stimulation of the sublingual mucosa is linked to an activation of a broad-spectrum mucosal and systemic immune response in the genitourinary tract. In particular, the response at the site of the bladder mucosa is both persistent and of high efficacy when the sublingual mucosa is stimulated [4–6]. This is the underlying mechanism of Uromune®.

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Uromune (Syner-Med [Pharmaceutical Products Ltd], Purley, UK/Inmunotek S.L., Madrid, Spain) is a sublingual spray, currently pre-licence in the phase III development stage and available under the named patient programme in the UK. It is composed of equal amounts of four common UTI-causing bacteria in a suspension of 10^9 inactivated whole bacteria/mL: *Escherichia coli*; *Klebsiella pneumoniae*; *Proteus vulgaris*; *and Enterococcus faecalis*.

Spanish retrospective studies comparing Uromune treatment with antibiotic therapy in women with recurrent UTIs have reported a significant decrease in UTI recurrence, with no reported side effects in any patient. The study reported a 90.28% (95% CI: 87.18–93.38) absolute risk reduction [7].

In the present study we report the prospective results of the first experience in the UK of using this new immunomodulation vaccine Uromune in an initial cohort of women with recurrent UTIs for whom conventional therapy has failed.

Patients and Methods

A total of 77 women with recurrent UTIs were identified. Their mean (range) age at commencement of therapy was 56 (18–87) years. Each woman had experienced a minimum of three episodes of microbiology-proven UTIs during the preceding 12 months. All the selected women had previously undergone various investigations, including cystoscopy and upper urinary tract imaging (either with CT or ultrasonography) to exclude any significant underlying pathology, such as bladder tumours or renal/bladder calculi. Antibiotic prophylaxis therapy had failed in all women prior to commencing Uromune and 50% of the selected women had also tried intravesical instillation therapies.

Each woman received 3 months of Uromune treatment. This was taken as a sub-lingual spray once a day. The patient was required to be 'nil by mouth' for the 2 h preceding and following each daily spray.

Prospective observational follow-up was conducted via a specialist nurse phone consultation for up to 12 months, and there was an ongoing direct contact telephone number for reporting any issues, including recurrent infections and side effects. An instruction letter for each patient's GP was also sent out.

Symptoms of infections, when reported, were confirmed by the patients' GPs, with a urinary sample analysed for microscopy culture and sensitivity prior to commencement of antibiotic therapy.

Ethics

This project was undertaken as a registered audit.

Results

Of the 77 women who commenced Uromune therapy, 75 successfully completed the course. One woman stopped Uromune after 2 weeks of therapy for lifestyle and personal reasons, in particular not being able to cope with the 2-h nil-by-mouth regime preceding and following spray administration. She also reported not liking the taste of the spray.

One woman stopped therapy after experiencing an allergic reaction (described below).

Of the 75 women who completed therapy, 59 women (78%) reported no subsequent UTIs during both the treatment and in the subsequent follow-up period (Fig. 1).

Of the 16 women who experienced a UTI recurrence, 14 (87%) were post-menopausal. The median (range) time to first recurrence was 2 (1–8) months (Figs 2 and 3).

Among the women with recurrences, *E. coli* grew in the urine culture of 12. The remaining women had mixed growth, *Pseudomonas*, *Klebsiella* and *Serratia marcescens*.

Adverse Reactions

One woman experienced an adverse reaction to Uromune. This woman had a history of an allergic rash to penicillin, trimethoprim, nitrofurantoin and ciprofloxacin, with underlying chronic kidney disease, multiple sclerosis and bilateral ureteric implantation for reflux. The woman developed a rash affecting her face and neck after 2 days of Uromune treatment. This resolved after stopping the therapy. She recommenced Uromune therapy and, 2 days later, the same rash-like reaction affecting her face and neck appeared. Throughout there was no evidence of airway compromise or anaphylaxis reaction. The woman took anti-histamines on both occasions to relieve her symptoms. On review, this woman permanently discontinued her treatment.

Fig. 1 Pie chart showing number of women with recurrent UTIs who remained infection-free and number experiencing another infection after commencing Uromune treatment.

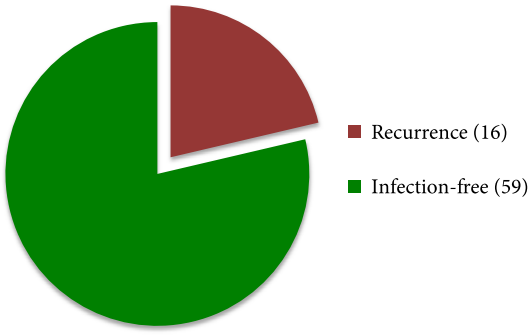


Fig. 2 Bar chart showing number of first recurrences at each month since commencement of Uromune treatment to date.

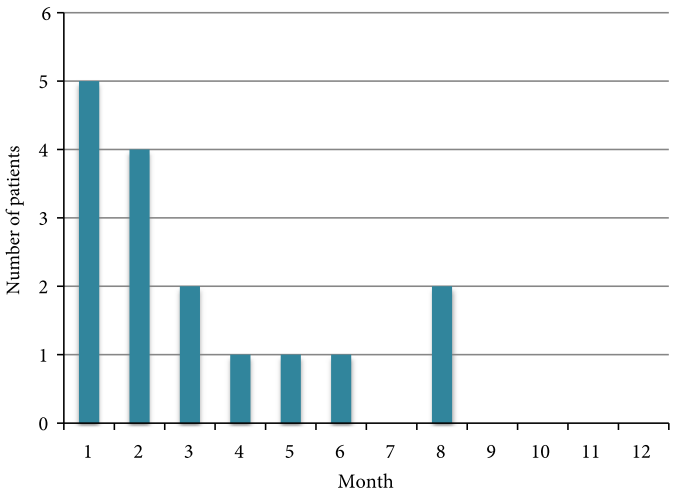
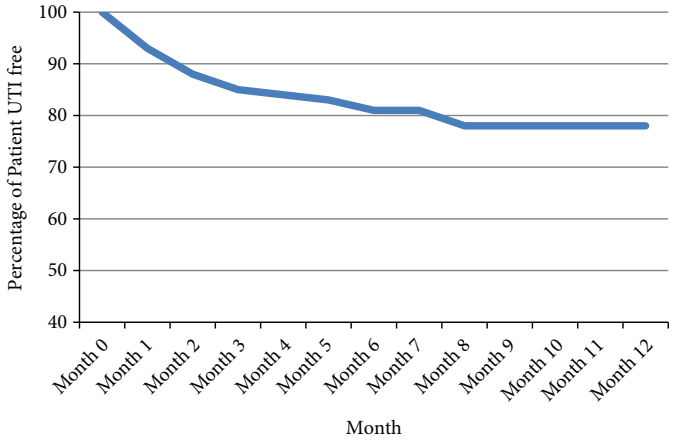


Fig. 3 Line chart showing percentage of patients remaining UTI-free since commencement of Uromune treatment.



A total of seven women (<10%) reported minor potential adverse reactions during their 3-month course of Uromune including: post nasal drip; stinging around mouth; pruritus over old BCG scar; pruritus over abdomen; intermittent abdominal pains; and mild nausea. One woman with underlying asthma had an asthma exacerbation 2 months into treatment, and temporarily paused her Uromune course. All these women recommenced or continued their Uromune treatment and completed the course with no repeat or worsening of the above symptoms.

Discussion

This initial cohort study suggests that Uromune is both safe and effective in women with recurrent UTIs, with the majority of the participants recruited remaining infection-free since commencement of treatment. This was achieved with a background of minimal reproducible side effects. Furthermore, anecdotally, patient satisfaction rates were high, in particular, with regard to the straightforward and pain-free administration of the treatment.

The majority of women with recurrences grew *E. coli* in their urine culture, in line with *E. coli* as the most predominant causative organism of UTIs. The rest had mixed growth, *Pseudomonas*, *Klebsiella* and *S. marcescens*; however, no one type of bacteria or resistance pattern was prevalent.

Interestingly, of the women who still experienced recurrences despite treatment, the majority were postmenopausal. In total, 50 of the 75 women who completed treatment were in a postmenopausal state, with 14 of these postmenopausal women experiencing a recurrence, meaning Uromune was successful in 72% of post-menopausal women in preventing further UTI recurrences. By contrast, of the 25 premenopausal women who completed Uromune treatment, only two experienced a recurrence, signifying that the vaccine was effective in 88% of premenopausal women at preventing further UTI recurrences.

This is in line with decreased immunity with age and the lower oestrogen state found in women post menopause and its link with decreased innate immunity via the loss of the commensal bacteria *Lactobacillus* and the loss of the acidic pH microenvironment within the vagina. This could very well be a further avenue of research to develop adjuvant therapies with Uromune. Currently, there is evidence that CO_2 ablation vaginal lasers may help rejuvenate this microenvironment, much like oestrogen therapy, restoring the lactic acid synthesis of commensal bacteria and the innate vaginal defence against UTIs [8–10]. Combination therapy, therefore, with both Uromune and a CO_2 ablation vaginal laser may provide better effectiveness at preventing UTI recurrence in postmenopausal women, and is a potentially novel avenue for further research.

As mentioned above, previous Spanish studies by Lorenzo-Gomez et al. on Uromune have also shown favourable results. In a cohort of 669 women with recurrent UTIs, their latest 2016 study [7] retrospectively compared the risk reduction of developing UTI recurrence between 3 months of Uromune prophylaxis and 6 months of antibiotic prophylaxis over a 1-year follow-up period. The antibiotics chosen were trimethoprim/sulfamethoxazole or nitrofurantoin, depending on renal function and sensitivities. The authors reported a shorter time to first recurrence in the antibiotic group, as well as a 90.28% (95% CI: 87.18–93.38) absolute risk reduction when using Uromune. They also reported finding no local or systemic side effects. Whilst the results from that study are more positive than those of the present study, the study by Lorenzo-Gomez et al. was limited by the retrospective manner in which it was performed, lacking the more accurate

outcomes associated with prospective explanatory controlled studies.

Uromune also has better efficacy when compared with previous immunomodulation therapies. One of the first oral immunomodulation therapies was Uro-Vaxom® (Terralab, Zagreb, Croatia). This tablet contained bacterial extracts of 18 uropathogenic *E. coli* strains. Previous studies [11] have reported a relative risk reduction of 0.61 (95% CI 0.48–0.78) when compared with placebo, but a recent multicentre double-blind control trial [12] showed no significant difference in UTI rates between UroVaxom and placebo in 451 patients. During that study, however, a low number of UTIs occurred. The study concurrently failed to show the effectiveness of nitrofurantoin prophylaxis (a previously well established outcome), thus the low number of UTIs may well have had an impact on the conclusions.

Overall, these results for Uromune satisfy two of the WHO Global Action Plan strategic objectives by reducing the incidence of infection and developing a potential new medicine in the form of a vaccine in order to reduce antibiotic resistance.

Limitations of the present prospective observational study include the relatively small number of patients recruited, in addition to the lack of a control group. To further progress our understanding of Uromune, further prospective studies involving larger groups of patients, with longer follow-up periods and conducted in a double-blind placebo-controlled manner, are required. A large international multicentre collaboration between Spain and the UK is currently underway, in which 240 women with recurrent UTIs have been recruited to a prospective double-blind randomized controlled trial comparing Uromune with placebo for a 2-year period.

In conclusion, the data from this prospective study appear to indicate that Uromune may have strong potential as a viable alternative therapy in the treatment of women with recurrent UTIs.

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Conflict of Interest

None declared.

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Abbreviation: MALT, mucosal associated lymphoid tissue.