



First experience in the United Kingdom of treating women with recurrent Urinary Tract Infections with the bacterial vaccine Uromune®

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Keywords:	Recurrent Urinary Tract Infection, Bacterial Vaccine, Immunomodulation
Abstract:	<p>Objectives: To determine the effectiveness of Uromune® in preventing recurrent urinary tract infections (UTIs) in women.</p> <p>Patients and methods: 77 women with microbiology proven recurrent UTIs were given 3 months of Uromune® sublingual vaccine. Follow up for up to 12 months prospectively recorded time to first UTI recurrence since treatment and adverse events.</p> <p>Results: 75 of 77 women 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 experienced a minimum of three or more episodes of UTI during the twelve-month period preceding. Proportionally, the majority of recurrences occurred in postmenopausal women. One patient had to stop treatment due to an adverse event (rash over face and neck).</p> <p>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 randomised control trial comparing Uromune® and placebo is currently underway.</p>

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First experience in the United Kingdom of treating women with recurrent Urinary Tract Infections with the bacterial vaccine Uromune®

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Conflicts of interest: None

Keywords: *Recurrent Urinary Tract Infection, Bacterial Vaccine, Immunomodulation*



Abstract

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

Patients and methods: 77 women with microbiology proven recurrent UTIs were given 3 months of Uromune® sublingual vaccine. Follow up for up to 12 months prospectively recorded time to first UTI recurrence since treatment and adverse events.

Results: 75 of 77 women 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 experienced a minimum of three or more episodes of UTI during the twelve-month period preceding. Proportionally, the majority of recurrences occurred in postmenopausal women. One patient had to stop treatment due to 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 randomised control trial comparing Uromune® and placebo is currently underway.

Introduction

Urinary tract infections are one of the most prevalent conditions worldwide, typically affecting a disproportionately larger number of women than men.

Recurrent UTIs are defined as “three or more episodes of UTI during a twelve month period” or “two or more 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. Such is the problem that the World Health Organisation (WHO) have implemented a Global Action Plan in 2015 to tackle antimicrobial resistance. The achievement of this goal by the WHO is via 5 strategic objectives quoted below: (2)

1. To improve awareness and understanding of antimicrobial resistance
2. To strengthen knowledge through surveillance and research
3. To reduce the incidence of infection
4. To optimise the use of antimicrobial agents
5. To develop the economic case of sustainable investment that takes account of the needs of all counties and increase investment in new medicines, diagnostic tools vaccines and other interventions.

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3 With UTIs attributing a large proportion of infections worldwide requiring
4 antibiotic use, there is rapidly growing research in Urinary Tract Infections. The
5 current and new preventative measures in the treatment of UTIs have recently
6 been reviewed. (3) One potential treatment option is via an immunomodulation
7 vaccine that utilises the patients' own immune system to prevent recurrent UTIs.
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10 The genitourinary tract utilises an innate and adaptive mucosal immune system
11 to fight against uropathogens. This belongs to the mammalian lymphoid organ
12 system, an immune system contributed by 80% of all immunocytes in the body
13 and made up of various different areas around the body. Immunocytes transit
14 through various mucosal associated lymphoid tissue (MALT) sites, thus
15 dissemination of immunity to various MALT sites is possible via the activation of
16 lymphocytes at one distant MALT site. (4) Various studies have found that
17 stimulation of the sublingual mucosa has been linked to an activation of a broad-
18 spectrum mucosal and systemic immune response in the genitourinary tract. In
19 particular the response at the site of the bladder mucosa is both persistent and of
20 high efficacy with the sublingual mucosa is stimulated. (4-6) This is the
21 underlying mechanism of Uromune®.
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23
24 Uromune® (Syner-Med (PP) Ltd UK, Immunotek S.L. Spain) is sublingual spray
25 currently pre-licence in the phase III development stage available under the
26 named patient program in the United Kingdom.
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29 It is composed of equal amounts of four common UTI causing bacterium;
30 *Escherichia Coli*, *Klebsiella Pneumoniae*, *Proteus Vulgaris* and *Enterococcus*
31 *Faecalis*, in a suspension of 10⁹ inactivated whole bacteria/ml.
32

33
34 Spanish retrospective studies comparing Uromune® treatment and antibiotics
35 therapy in women with recurrent UTIs have reported a significant decrease in
36 UTI recurrence with no reported side effects in any Uromune® patients. The
37 study reported a 90.28% (87.18-93.38) absolute risk reduction. (7)
38

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40 Here we introduce the prospective study on the first experience in the United
41 Kingdom of this new immunomodulation vaccine Uromune® in an initial cohort
42 of women with recurrent UTIs who have failed conventional therapy.
43

44 **Patients and Methods**

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46 77 women with recurrent UTIs were identified. The average age at
47 commencement of therapy was 56 years, ranging from 18 to 87 years. Each
48 woman during the 12 month preceding suffered with a minimum of 3 or more
49 episodes of microbiology proven urinary tract infections. All the selected women
50 have previously undergone various investigations including cystoscopy and
51 upper urinary tract imaging (either with Computerised Tomography or
52 Ultrasound) to exclude any significant underlying pathology such as bladder
53 tumours or renal/bladder calculi. All women prior to commencing Uromune®
54 had failed antibiotic prophylaxis therapy. 50% of selected women had also tried
55 intravesical instillation therapies.
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3 Each woman received 3 months of Uromune®. This was taken as a sub-lingual
4 spray once a day. The patient was required to be nil by mouth for the 2 hours
5 preceding and following each daily spray.
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8 Prospective observational follow up was for up to 12 months via a specialist
9 nurse phone consultation and an on-going direct contact number to report any
10 issues, including recurrent infections and side effects. An instruction letter for
11 the patients General Practitioner was also sent out for each patient.
12

13 Infections symptoms when reported were confirmed via the patients General
14 Practitioner with a urinary sample analysed for microscopy culture and
15 sensitivity prior to commencement of antibiotic therapy.
16

17 **Results**

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19 Of the 77 women who commenced Uromune® therapy, 75 successfully
20 completed the course. One woman stopped Uromune® after 2 weeks into
21 therapy due to lifestyle and personal reasons, in particular not being able to cope
22 with the 2 hour nil by mouth regime preceding and following spray
23 administration. She also reported not liking the taste of the spray.
24 One woman stopped therapy after experiencing an allergic reaction (described
25 below).
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29 Of the 75 women who completed therapy, 59 women (78%) reported no
30 subsequent UTIs during both the treatment and in the subsequent follow up
31 period. This is shown in figure 1.
32

33
34 Of the 16 women who experienced a UTI recurrence, 14 (87%) were post-
35 menopausal.
36

37 The median time to first recurrence was 2 months, ranging from 1 – 8 months
38 (Figure 2 and Figure 3).
39

40 For the women with recurrences, 12 in their urine cultures grew *Escherichia Coli*.
41 The rest had Mixed Growth, *Pseudomonas*, *Klebsiella* and *Serratia Marcescens*.
42

43 Adverse reactions

44
45 One patient experienced an adverse reaction to Uromune®. The patient had a
46 history of an allergic rash to penicillin, trimethoprim, nitrofurantoin and
47 ciprofloxacin with underlying chronic kidney disease, multiple sclerosis and
48 bilateral ureteric implantation for reflux. The patient developed a rash affecting
49 her face and neck after 2 days of Uromune®. This resolved upon stopping the
50 therapy. The patient recommenced Uromune® therapy and 2 days later, the
51 same rash like reaction affecting her face and neck appeared. Throughout there
52 was no evidence of airway compromise or anaphylaxis reaction. The patient both
53 times took anti-histamines to relieve her symptoms. The patient on review
54 permanently discontinued her treatment.
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3 7 patients (<10%) reported minor potential adverse reactions during their 3
4 month course of Uromune®, which are listed below:

- 5 • Post nasal drip
- 6 • Stinging around mouth
- 7 • Pruritus over old BCG scar
- 8 • Pruritus over abdomen
- 9 • Intermittent abdominal pains
- 10 • Mild nausea

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13 One patient with underlying asthma had an asthma exacerbation 2 months into
14 treatment, temporarily pausing her Uromune® course.

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17 Importantly, all the above patients recommenced or continued their Uromune®
18 treatment and completed the course with no repeat or worsening of the above
19 symptoms.

20 21 22 23 **Discussion**

24
25 This initial cohort suggests that Uromune® is both safe and effective in women
26 with recurrent UTIs, with a majority of recruited patients remaining infection
27 free since commencement of treatment. This was achieved in the background of
28 minimal reproducible side effects. Furthermore, anecdotally, patient satisfaction
29 rates were also high, in particular with how straight forwards and pain-free the
30 administration of the treatment is.

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33 The majority of women with recurrences grew *Escherichia Coli*, in line with *E Coli*
34 as the most predominant causative organism of urinary tract infections. The rest
35 had Mixed Growth, *Pseudomonas*, *Klebsiella* and *Serratia Marcescens*. However
36 there were no themes to the type of bacteria or the resistance patterns.

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39 Interestingly, for the women who still experienced recurrences despite
40 treatment, the majority were postmenopausal. In total, 50 of the 75 women who
41 completed treatment were in a postmenopausal state, with 14 of these
42 postmenopausal women experiencing a recurrence, meaning Uromune® was
43 successful in 72% of post-menopausal women in preventing further UTI
44 recurrences. On the other hand, of the 25 premenopausal women who completed
45 Uromune® treatment, only 2 of them experienced a recurrence, signifying that
46 the vaccine was effective in 88% of premenopausal women at preventing further
47 UTI recurrences.

48
49 This is in line with decreased immunity with age and the lower oestrogen state
50 found in women postmenopause and its link with decreased innate immunity via
51 the loss of the commensal bacteria *Lactobacillus* and the loss of the acidic pH
52 microenvironment within the vagina. This could very well be a further avenue of
53 research to develop adjuvant therapies with Uromune®. Currently there is
54 evidence that CO₂ ablation vaginal lasers may help rejuvenate this
55 microenvironment, much like oestrogen therapy, restoring the lactic acid
56 synthesis of commensal bacterial and the innate vaginal defence against UTIs. (8-
57 10) Combination therapy therefore with both Uromune® and a CO₂ ablation
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3 vaginal laser may provide better effectiveness at preventing UTI recurrence in
4 postmenopausal women, and is a potentially novel avenue for further research.
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7 As mentioned above, previous Spanish studies by Lorenzo-Gomez et al (7) on
8 Uromune® have also shown favorable results. In a cohort of 669 women with
9 recurrent UTIs, their latest 2016 study retrospectively compared the risk
10 reduction of developing UTI recurrence between 3 months of Uromune®
11 prophylaxis and 6 months of antibiotic prophylaxis over a 1 year follow up
12 period. The antibiotics chosen were Trimethoprim/sulfamethoxazole or
13 Nitrofurantoin depending on renal function and sensitivities. The authors
14 reported a shorter time to first recurrence in the antibiotic group, as well as a
15 90.28% (87.18-93.38) absolute risk reduction when using Uromune®. The
16 authors also reported finding no local or systemic side effects. Whilst the results
17 from their study are more positive compared to our data reported above, their
18 study was limited by the retrospective manner in which it was performed,
19 lacking the more accurate outcomes associated with prospective explanatory
20 controlled studies.
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24 Uromune® also has better efficacy when compared with previous
25 immunomodulation therapies. One of the first oral immunomodulation therapies
26 was Uro-Vaxom® (Terralab, Croatia). This tablet contained bacterial extracts of
27 18 uropathogenic *Escherichia Coli* strains. Previous studies (11) have reported a
28 relative risk reduction of 0.61 (95% CI 0.48-0.78) when compared against
29 placebo. However a recent multicentre double blind control trial (12) showed no
30 significant difference in UTI rates between UroVaxom® and placebo in 451
31 patients. However during that study, a low number of UTIs occurred. This
32 concurrently failed to show the effectiveness of Nitrofurantoin prophylaxis (a
33 previously well established outcome), thus the low number of UTIs may well
34 have impacted on the conclusion.
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38 Overall, these results for Uromune® satisfies two of the WHO Global Action Plan
39 strategic objectives by reducing the incidence of infection and developing a
40 potential new medicine in the form of a vaccine in order to reduce antibiotic
41 resistance.
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44 The limitations of this study include the relative small numbers of patients
45 recruited in addition to the lack of a control group in this prospective
46 observational study.

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48 Therefore in order to further progress our understanding on Uromune®, further
49 prospective studies involving larger groups of patients with longer follow-ups
50 periods in a double blinded placebo controlled manner are required. Currently
51 underway is a large international multicentre collaboration between Spain and
52 the United Kingdom, where 240 women with recurrent UTIs have been recruited
53 into a randomised control trial comparing Uromune® with placebo in a
54 prospective double blind format for a 2 years period.
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Overall, the data from this prospective study appears to indicate that Uromune® may harbor strong potential in becoming a viable alternative therapy in the treatment for women with recurrent UTIs.

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Conflicts of interest: None

Ethics: This project was undertaken as a registered audit

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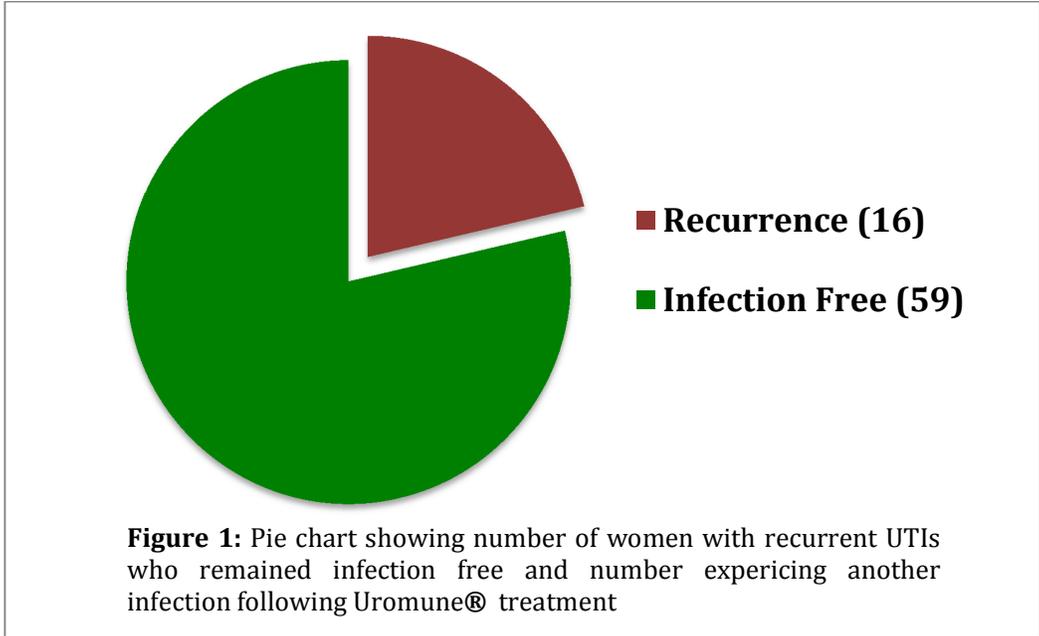
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Peer Review

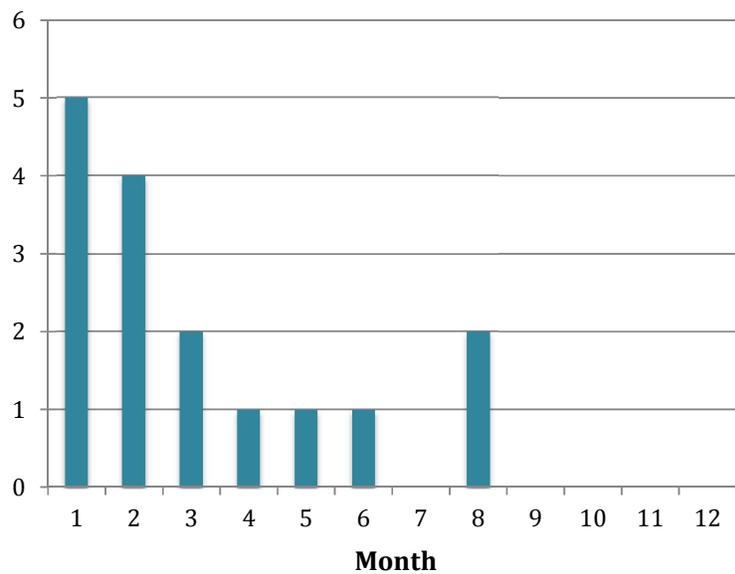
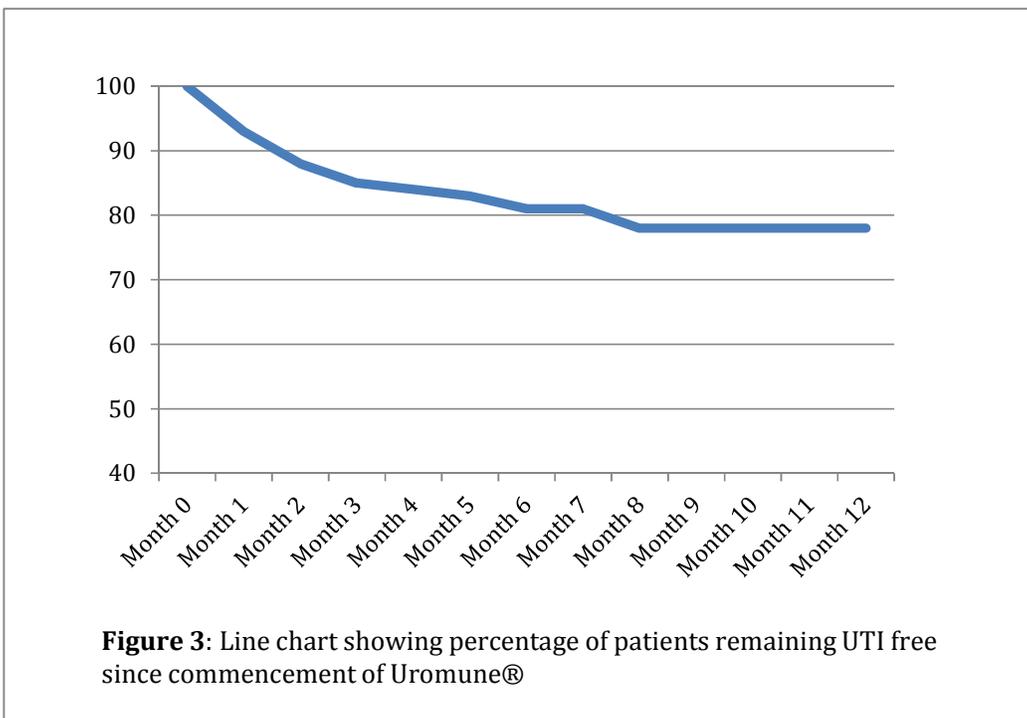


Figure 2: Bar chart showing number of first recurrences at each month since commencement of Uromune® to date

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