# RECURRENT URINARY TRACT INFECTIONS: CAN IMMUNOACTIVE PROPHYLAXIS IMPROVE DISEASE MANAGEMENT IN HEALTHY WOMEN?

## Narrative Summary of Selected Presentations given at the OM Pharma/Vifor Pharma URO-VAXOM® Summit, held in Buenos Aires, Argentina, on 26th–27th April 2014

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**Disclosure:** The authors are global consultants of OM/Vifor Pharma Company, Meyrin, Switzerland.
**Acknowledgements:** Writing assistance was provided by Ewen Legg, ApotheCom ScopeMedical.
**Support:** The publication of this article was funded by OM/Vifor Pharma. The views and opinions expressed are those of the authors and not necessarily those of OM/Vifor Pharma.
**Citation:** EMJ Urol. 2014;1(Suppl 2):22-28.

## SUMMARY

This educational summit, supported by an independent grant from OM/Vifor Pharma, brought together experts in the field of urology and gynaecology from Europe and Latin America to meet and discuss the cutting edge management of patients suffering from recurrent urinary tract infections (rUTIs). The meeting included plenary lectures as well as workshops and interactive sessions, allowing delegates and presenters to debate the most pressing international and local issues in the field.

UTIs are one of the most prevalent bacterial infections and are the most common type of infection in healthy adult women, affecting 50% of them at least once in their lifetime.[1] The level of antibacterial resistance in common uropathogenic organisms is reaching alarming levels[2] and the importance of prophylaxis in the context of increasing resistance cannot be overstated. The current three-tiered approach taken by the European Association of Urology (EAU) for UTI prevention consists of: counselling and behavioural modification, followed by non-antimicrobial prophylaxis, and eventually antimicrobial prophylaxis.[3] For many women, counselling and behavioural modification will not be enough to prevent rUTIs, resulting in a need for effective non-antimicrobial therapies which spare antibiotic use and reduce the risk of engendering further resistance in uropathogens. OM-89, a bacterial-lysate-based therapy, currently has the grade of recommendation B in the EAU guidelines for non-antimicrobial prevention of rUTI in otherwise healthy women.[3] In the following report we will summarise the putative immunostimulatory mechanism of OM-89 and review the evidence for its efficacy in preventing rUTIs in healthy pre and post-menopausal women.

## IMMUNOSTIMULATORY MODE OF ACTION OF OM-89

The host defences of the urinary tract can be divided into first and second lines of defence. The first line of defence is further subdivided into mechanical defences (the physical barrier of the uroepithelium and urinary flow) and innate aspecific immunity. Innate immunity is congenital, and characterised by a rapidly mounted inflammatory response. It is mediated via pattern recognition receptors (PRRs), such as Toll-like receptors (TLRs), which recognise pathogen-associated molecular patterns (PAMPs) and recruit phagocytic leukocytes

and granulocytes.[4] Perhaps the most well-known PAMP is lipopolysaccharide (LPS), which has long been recognised as a potent inducer of inflammatory response in mammals, which is recognised by the PRR TLR4. The second line of defence is adaptive/specific immunity. Adaptive immunity responds to specific pathogen-derived antigens with a targeted response. It involves multiple cell classes and is characterised by a slow activation, though responses may be rapid in later stages. The stages of adaptive immunity include: uptake of antigens by antigen-presenting dendritic cells (DCs); activation of T cells; B cell formation (conveying humoral immunity); and homing of immune cells.

## Challenges for the Immunostimulatory Approach

Direct stimulation of the immune system has been proposed as an alternative to antibiotic repeated treatment cycles and prophylaxis for UTIs. One of the principal challenges to this approach is posed by the variety of infective agents responsible for UTI. Although the vast majority (approximately 80%) of uncomplicated cystitis is caused by uropathogenic *Escherichia coli* (UPEC),[5,6] there are thousands of UPEC clones/strains, each with a unique antigen profile. This makes the selection of a single antigen likely to lead to broad immune response against UPEC infection challenging.[7] Attempts have been made at vaccination using single antigens shared by the majority of UPEC strains, such as the adhesion protein FimH or specific iron-uptake receptors. Inoculation with the virulence factor FimH has shown some success *in vivo*.[8] However, this has yet to translate to a workable human vaccine, perhaps due to FimH expression being subject to phase variation, allowing evasion of the humoral response.[7]

Iron uptake is essential for bacterial infection and vaccines against iron-uptake receptors have shown some promising results in *in vivo* models of sepsis[9] and have elicited immune response in the mouse kidney.[10] However, protection against UTI was not conferred by immunisation against iron-uptake receptors, likely due to a lack of detectable levels of immunoglobulin A (IgA) in the bladder.[10] Data on the role of the adaptive immune system (AIS) in acute lower UTI are sparse; however, results suggest it is less important than in related conditions such as pyelonephritis.[7] This may be a factor in the current lack of success with antigen-specific vaccination, suggesting another approach may be required. The use of extracts from inactivated UPEC strains is one such alternative approach. These extracts contain a multitude of antigens and PAMPs likely to facilitate activation ofboth the innate and AIS.[11] In the case of OM-89, the extract is comprised of the lysate of 18 UPEC strains and has shown efficacy in rUTI prophylaxis. Experimental studies investigating activation of both the innate and AIS by OM-89 have now generated evidence of activation at multiple stages of the immune response.

## Activation of the Innate Immune Response by OM-89

*In vitro* studies investigating the effects of OM-89 exposure on human cell lines expressing specific PPR (TLRs or Nod-like receptors) reveal a concentration-dependent activation of human TLR2 and TLR4.[12] There is extensive evidence for the role of TLR4 in the response against UTIs.[7,13] Both OM-89-induced stimulation of murine spleen cells - a key source of macrophages for the innate immune system[14] - and increased metabolic and phagocytic activity in circulating human leukocytes, isolated from peripheral blood, following incubation with OM-89 have been demonstrated *in vivo*. Furthermore, there was a 30% reduction in spontaneous apoptosis of human granulocytes incubated with OM-89, suggesting a mechanism involving both activation of the innate immune system and perpetuation of its activity.[15]

## Activation of the Adaptive Immune Response by OM-89

Antigen-presenting DCs are activated following PAMP recognition by PRRs and are a crucial bridge between the innate and AIS.[11] Circulating DCs capture and process antigens in the periphery before migrating to lymphoid organs and releasing cytokines to initiate adaptive immune responses.[16] Human monocyte-derived DCs exposed to OM-89 *in vitro* show a concentration-dependent increase in expression of the co-stimulatory protein CD83,[17] an important marker of DC maturation.[18] The role of mature DCs in stimulating T helper cell proliferation and interferon gamma production provides a possible mechanism for the activation of adaptive immunity by OM-89.[17,19] OM-89 has been shown to be an activator of polyclonal murine B lymphocytes.[20,21] In mice, both intraperitoneal and oral application of OM-89 stimulate production of antibodies, which bind strains of *E. coli* present in the OM-89 lysate, and immunogenicity has been

localised to the urogenital tract following repeated oral administration.[21,22] Increased levels of total and strain-specific IgG and IgA were detected in the supernatant of cell culture prepared from the urogenital tract of immunised mice, suggesting the creation of a protective barrier at the mucosa level of the urinary tract.[20–22]

In a murine model of *E. coli* infection-induced cystitis, oral pre-treatment with OM-89 led to a concentration-dependent reduction in the number of viable bacteria, as measured by colony forming units.[22] Notably, serum from mice treated with oral OM-89 was active not only against all 18 strains present in the lysate but also against a number of other uropathogenic microorganisms and other unrelated bacteria.[15,22,23] Stimulation of adaptive immunity has also been demonstrated in a human study of 38 paediatric patients with rUTI. Administration of OM-89 alongside antibiotic prophylaxis led to a 65% (p=0.02) increase in secretory IgA in urine at the end of the 6-month study. This increase has not been seen in the control group.[24] Finally, there is histological evidence of the protective effects of oral therapy with OM-89 in a murine model of LPS-induced cystitis. Mice treated for 10 days before induction of cystitis had a significant reduction in their bladder inflammatory index compared with untreated mice.[25]

### Summary

Oral treatment with OM-89 activates an innate immune response and stimulates maturation of DCs - the key bridging cells between innate and adaptive immunity. Adaptive uropathogen-specific immunity has been located to the urinary tract, and reduced viability of *E. coli* and reduced LPS-induced inflammation has been demonstrated. Hence, the above data provide a viable theoretical framework for the immune system cascade, leading from oral treatment to activity in the bladder and clinical efficacy of OM-89 against rUTI.

## CLINICAL EFFICACY OF OM-89 IN HEALTHY PRE-MENOPAUSAL WOMEN

Evidence for the clinical efficacy of OM-89 prophylaxis against rUTI exists at various levels, up to and including meta-analyses. Six randomised controlled trials (RCTs) of OM-89 versus placebo have been carried out in otherwise healthy adults - mainly women from 18 years of age. The majority of these featured a 3-month dosing period with patients followed up to 6 months from study commencement,[26–29] with one study extending follow-up to 11 months.[30] There was also a single 12-month study investigating the efficacy of using booster doses for longer term prophylaxis.[31] The trials demonstrated a mean reduction in recurrences of 30–50% with good tolerability.[26–31]

### Illustrative Data from Single Randomised Trials

Study design, safety, and efficacy were broadly similar in the 6-month randomised studies. In the Schulman et al.[27] trial, 160 patients (84% female, mean age 45.2 years), with a history of ≥2 UTIs in the preceding 12 months, were enrolled. A highly significant, almost 50%, decrease (58 versus 114, OM-89 and placebo, respectively, p<0.0001) in the number of UTIs (defined as $10^5$ bacteria/mL urine) was achieved at 6-month follow-up. There was a similarly marked reduction in mean days spent on antibiotic treatment in the group receiving OM-89 prophylaxis (3.0 versus 6.3 days, OM-89 and placebo, respectively, p<0.0001). Improvements in typical signs and symptoms were also reported, with a favourable benefit–risk profile. A chi-square test on all data to determine overall treatment benefit against placebo gave a significant outcome in favour of OM-89.[27]

In the single 12-month study carried out thus far, patients received 3 months initial treatment followed by a 3-month observation period. During months 7–9, daily booster doses were administered for 10 days and patients were followed up for a further 3 months. In total, 453 female patients aged 18–65 years with a history of ≥3 UTIs in the preceding 12 months were enrolled. Over the 12-month study period, the cumulative rate of UTI was 34% lower in the group treated with OM-89 (p<0.003). The number of patients who did not suffer a recurrence was also higher in the OM-89 group (55% versus 42%, OM-89 and placebo, respectively, p=0.0013) and antibiotic consumption was reduced by 13% (p=0.005). As with the above shorter duration trial, OM-89 was well tolerated.[31]

The above evidence from single trials shows OM-89 to be a well-tolerated UTI prophylactic and antibiotic-sparing therapy with efficacy over 6 and 12 months. Data from the above trials have been synthesised in three meta-analyses.[32–34] Meta-analyses represent the highest level of evidence available to clinicians and clinical scientists, allowing amelioration of bias which may be present in single studies and, in some cases,

revealing novel efficacy or safety-related data due to the increased statistical power derived from larger group sizes.

## Meta-Analysis of the Efficacy of OM-89 and other Prophylactic Measures

In 2002, Bauer and colleagues[32] carried out a meta-analysis which included data from women enrolled in the five RCTs of 6-month duration mentioned above;[26–29,32] data from 601 women were analysed in total. OM-89 was found to be superior in reducing UTIs across all studies versus placebo (Figure 1). Symptoms of UTI, dysuria, bacteriuria, and leukocyturia, were all found to be significantly improved in patients treated with OM-89. Improvements compared with placebo were found to be both statistically significant and clinically relevant for all outcome measures mentioned above. The Mann–Whitney summary statistic also demonstrated the superiority of OM-89 with a medium-to-large overall effect size (0.684). Compliance and tolerability were deemed good across all trials by study investigators.[32]

In a second meta-analysis by Naber and colleagues,[33] data from the 12-month study - alongside those from four of the 6-month studies - were deemed suitable for inclusion, comprising 1,000 adult patients.[27–29,31,33] Results were similar to the above analysis, with a mean reduction in the number of UTIs across all studies of 36% at the 6-month time point ($p<0.00001$) and 39% at combined study endpoint in patients treated with OM-89 ($p<0.00001$). More OM-89 patients were free of UTI at combined study endpoint (65% versus 45%, OM-89 versus placebo, $p<0.001$) and antibiotic consumption was significantly reduced with a small-to-medium effect size (standardised mean difference, -0.29). As in the Bauer meta-analysis,[32] there were significant improvements in symptoms and laboratory findings. The side-effect profile of OM-89 was comparable with placebo, with slightly more frequent adverse events in the OM-89 group compared with placebo (+0.8%).

A key result from the Naber et al.[33] study came from the plotting of the mean number of episodes of UTI, with OM-89 as a function of the number of episodes with placebo, which revealed that the studies with the largest number of UTIs in the placebo group were those showing the largest benefit from OM-89. This suggests that patient groups that are more likely to have multiple incidents of recurrence are most likely to benefit from OM-89. It is also worth noting that having a UTI within the previous 12 months is a risk factor for emergence of multi-drug resistant (MDR) infection.[2] Thus, OM-89 may reduce infection most in the group at highest risk of MDR infection, and further improve antibiotic stewardship as a result.[33]

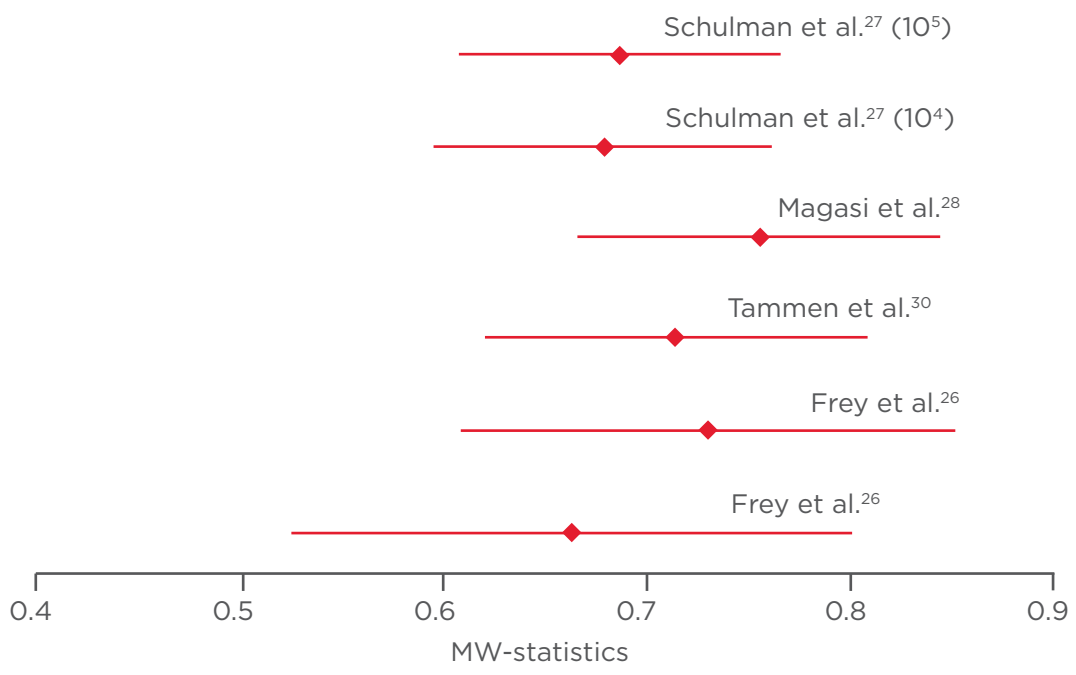


**Figure 1: Mann–Whitney (MW) statistical analysis of placebo-controlled trials of OM-89 prophylaxis.**
*Adapted from Bauer et al.[32]*

The final meta-analysis included a number of other prophylactic measures alongside OM-89; 5,413 records were identified and included 17 studies with data for 2,165 patients. Seven prophylactic strategies were identified including: OM-89, vaginal vaccine, vaginal oestrogens, cranberry, and acupuncture. OM-89 reduced UTI recurrence (RR=0.61, 95% CI: 0.48–0.78), with a promising efficacy and a good safety profile. The other results were considered tentative and requiring further corroboration. Vaginal vaccine slightly reduced UTI recurrence (RR=0.81, 95% CI: 0.68–0.96). Vaginal oestrogens showed a trend towards preventing UTI recurrences (RR=0.42, 95% CI: 0.16–1.10) and vaginal irritation in 6–20%. Cranberry decreased UTI recurrence and acupuncture reduced recurrences (RR=0.53, 95% CI: 0.33–0.83 and RR=0.48, 95% CI: 0.29–0.79, respectively).[34]

### Summary

Data from six placebo-controlled trials, and three meta-analyses, indicate that OM-89 is a non-antibiotic prophylactic strategy showing robust efficacy against rUTI in healthy adults, mainly women. OM-89 prophylaxis shows promising results as an antibiotic sparing strategy, and appears to have greatest efficacy in the group of women with highest clinical need.

## CLINICAL EFFICACY IN HEALTHY POST-MENOPAUSAL WOMEN

There is an increase in the risk of UTI and bacteriuria with increasing age. Post-menopausal women can be subdivided into healthy 50–70-year-olds who are neither institutionalised nor catheterised (lower risk) and elderly institutionalised women who are, in many cases, catheterised.[35] Physiological and clinical features of the latter group, particularly catheterisation, require consideration and affect treatment options and outcomes. In the following section we will concentrate on the former group of healthy post-menopausal women.

### Risk Factors for UTIs in Post-Menopausal Women

The predisposing factors for rUTI vary with age. In pre-menopausal women, factors relating to sexual intercourse such as increased frequency, use of spermicide, and having a new sexual partner are predominant. While in post-menopausal women, the predominant factors are age related, including oestrogen deficiency, urinary incontinence, and pelvic organ prolapse with voiding dysfunction. In post-menopausal women, oestrogen deficiency can lead to alterations of the urogenital tract mucosa and promote more frequent UTI. There is a putative link between decreased oestrogen, reduced vaginal lactobacilli, increased vaginal pH, and increased colonisation with *Enterobacteriaceae* coming from the peri-anal region. However, it is important to note that this relationship is controversial due to the presence of conflicting data.[35] Older women with rUTI are likely to have been exposed to antibiotics for longer periods which may contribute to increased vulnerability to infections.[36] Antibiotics, by eradicating the periurethral and vaginal flora, may inadvertently enable colonisation, and hence infection, by new uropathogens. Theoretically, older patients could also be more prone to infections due to the effects of ageing on the immune system allowing uropathogens to more easily colonise the uroepithelium.

### Prophylaxis Against rUTIs in Post-Menopausal Women

The theoretical higher risk of rUTI in post-menopausal women makes prophylaxis a key strategy in this group. We have already mentioned the three-tiered approach to prevention, recommended by the EAU. This approach, 1) employing counselling and behavioural modification; 2) non-antimicrobial prophylaxis; and 3) antimicrobial prevention, is aimed at sparing antibiotic use and preventing the development of resistance.[3] Risk factors in post-menopausal women tend to be related to age rather than to modifiable behaviours (e.g. spermicide use in younger women). As a result, the first tier of EAU recommendations may be less effective in post-menopausal women, leading to a greater need for non-antimicrobial prophylaxis, including prevention with immunoactive therapy such as OM-89.

Some of the trials summarised above[27,31] enrolled post-menopausal participants; however, only a single study investigating OM-89 prophylaxis specifically in post-menopausal women with rUTI has been carried out.[37] This was a small, observational, open-label, active control study with a duration of 9 months. The UTI rate was determined retrospectively for the 6 months before treatment initiation. Patients received a single capsule of OM-89 daily for 3 months, followed by a 3-month observation then 10 days of booster

dosing for each of the last 3 months. Subjects were post-menopausal women (n=55; mean age, 66.3 years) with rUTI, including some who were not receiving hormone therapy. Efficacy outcomes included the number of recurrences before and after the immunotherapy and the severity of dysuria.[37] The incidence of recurrences fell from 3.4±1.14 in the 6 months preceding oral immunotherapy to 1.8±1.59 during the 9-month monitoring phase, representing a 64.7% reduction in the recurrence rate in the 55 women receiving oral therapy. In a subgroup of women with higher risk of infection (n=41) (defined as having had >2 UTIs in the previous 6 months), mean rate of recurrences fell from 3.9±0.81 to 2.0±1.66: close to a 70% reduction.[37] This result agrees with the results from Naber et al.,[33] suggesting that patients with the highest rate of UTI may benefit the most from OM-89 prophylaxis.[33]

### Summary

The higher risk of UTI in post-menopausal women and the nature of risk factors, which are less amenable to amelioration with behavioural measures, make non-antimicrobial prophylaxis a key tool in preventing infection and sparing antibiotic use in this population. Results from the single study on OM-89 prophylaxis carried out in this group concur with those carried out in healthy adults, mainly women. Importantly, high-risk patients with a recent history of UTI showed a greater reduction in recurrences, suggesting that patients with the greatest clinical need, and at highest risk of urological infection, may benefit most from OM-89 prophylaxis.

## CONCLUSION

The immune-stimulant oral prophylactic OM-89 activates both the innate and AIS, boosting host defences against UTI. OM-89 has shown efficacy in both healthy pre and post-menopausal women affected by rUTI, reducing the number of recurrences and laboratory signs and symptoms of cystitis. The increased effect reported in high-risk individuals combined with OM-89's antibiotic sparing qualities, make this prophylactic measure an important resource for physicians tasked with antibiotic stewardship in the context of increasing antibiotic resistance of uropathogens.

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