The place of OM-89* immunoprophylaxis in the management of recurrent cystitis

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TABLE OF CONTENTS

INTRODUCTION **3**

URINARY TRACT INFECTIONS **4**

Definition and epidemiology 4

Pathophysiology 5

Impact on quality of life and unmet need 5

Treatment and prevention of urinary tract infections: what do guidelines recommend? 6

PREVENTION OF RECURRENT LOWER UTIS – INTRODUCTION ON OM-89 ..... **8**

Composition and presentation 8

Clinical indications 8

Dosage and administration 8

Limitations for use 9

MECHANISM OF ACTION **10**

Chemical lysis 10

Host innate immunity 10

Host adaptive immunity 11

OM-89 in vitro effects 11

OM-89 in vivo effects 12

KEY CLINICAL EVIDENCE **13**

Efficacy under conventional dosing scheme of 90 days 14

Long-term efficacy 20

Efficacy under booster dosage 21

Special patient populations 26

Systematic review and meta-analysis 32

IMPACT ON PATIENT QUALITY OF LIFE **37**

SAFETY PROFILE **38**

REFERENCES **40**

Introduction

Uncomplicated lower urinary tract infections (UTIs) are among the most frequent bacterial infections, especially in women, and recurrences are common. These recurrences considerably affect patient quality of life and represent an enormous financial and economic burden. The main causative pathogen involved in recurrent lower UTIs is *Escherichia coli* (*E. coli*), responsible for up to 80% of all infections.

This document gives a brief overview of OM-89 including its mode of action and key clinical study results in the prevention of recurrent UTIs. Although our understanding has grown considerably over the past 20 years, studies are still on-going in order to better understand the treatment and how it works.

Urinary tract infections

DEFINITION AND EPIDEMIOLOGY

Uncomplicated urinary tract infections (UTIs) are among the most common bacterial infections, especially in women of all ages. Almost half of all women experience at least one UTI during their reproductive years,[1] and this figure increases to 60% in postmenopausal women.[2]

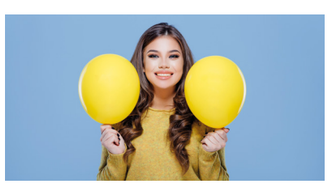
Classic symptoms of acute lower UTI (cystitis) include dysuria, urinary frequency, and urgency, with suprapubic pain. Given these signs, the likelihood of uncomplicated UTI is >90%, provided that no vaginal discharge or irritation is present.[3]

Recurrent lower UTIs are defined as two UTIs within 6 months, or more traditionally, as ≥3 positive cultures within the preceding 12 months.[4] This is estimated to occur in 25% of women with a history of UTIs.[5]

A number of risk factors have been identified for recurrent UTIs (Table 1). In all age groups, a history of UTIs, blood group antigen non-secretor status, anatomic abnormalities, trauma manipulation, diabetes, obesity, antibiotic use and vaginal infection all contribute to increased UTI risk.[6,7] Diabetes increases urine glucose concentrations, facilitating the growth of pathogenic bacteria.[7-9] Additionally, when the first infection is caused by *E. coli*, women appear to be more likely to develop a second UTI within six months compared with those whose first UTI was due to another organism.[10] In young and premenopausal women, several risk factors are linked to sexual habits including the use of diaphragms, spermicides, different sexual partners and frequent sexual activity, in addition to hygiene, all of which can disrupt the vaginal microbiota, allowing for adverse bacterial colonization.[6,7,10,11] The association between frequency of sexual intercourse and UTIs is particularly strong, with women who have had sexual intercourse more than nine times in the previous month, demonstrating a ten-fold increase in UTI incidence.[6,11] In postmenopausal and elderly women, risk factors include estrogen deficiency, genitourinary syndrome of menopause, cystocele, increased post-void urine volume, incontinence, urine catheterization and urogenital surgery have all increase the risk of recurrent UTIs.[6-8,12] Estrogen maintains the normal vaginal microbiota, in addition to maintaining vaginal muscle volume; lower levels are associated with a disrupted microbiota and increased risk of genital prolapse.[8,12]

Table 1

Risk factors for recurrent UTIs in women		
All ages	*Young and premenopausal*	*Postmenopausal and elderly*
• Personal/family history of UTIs • Non-secretor status • Anatomic abnormality • Trauma manipulation • Diabetes • Obesity • Antibiotic use • Vaginal infection	• Sexual activity • New sex partner in past year • Diaphragm/spermicide use • Antimicrobial use • Pregnancy	• Lack of estrogen • Genitourinary syndrome of menopause • Post-void residual urine • Cystocele • Incontinence • Catheterization • Urogenital surgery



PATHOPHYSIOLOGY

The main causative pathogen involved in recurrent lower UTIs is *Escherichia coli* (*E. coli*), which is responsible for up to 80% of all infections, with *Staphylococcus saprophyticus* and different aerobic Gram-negative germs (*Proteus mirabilis* and *Klebsiella spp.*) accounting for 5-15% and 5-10% of lower UTIs, respectively (Table 2).[13]

E. coli causes infections by adhering to, invading, and replicating in the umbrella cells of the bladder epithelium. Replication is facilitated by inflammation, leading to increased bacterial survival and invasion of the deeper layers of the urothelium. **These urothelial cells become reservoirs where pathogens persist in a quiescent state as a possible source of recurrent UTIs.**[13,14] This reservoir is undetected by immune surveillance mechanisms and protected from antibiotics, aided by the bladder epithelium permeability barrier.[14,15] Signals including epithelial turn over may trigger bacterial replication and the development of new acute UTIs.[14,15]

Table 2

Most common community and nosocomial urinary tract infection pathogens	
• *Uropathogenic Escherichia coli (UPEC)* • *Staphylococcus saprophyticus* • *Proteus spp.* (more common in men)	• *Providencia spp.* (more common in men) • *Klebsiella spp. Enterococcus faecium*

IMPACT ON QUALITY OF LIFE AND UNMET NEED

Patients with recurrent UTIs experience high symptom burden, and reduced quality of life (QoL) compared with the general population.[16,17] Reductions in physical QoL, particularly in the form of body pain is experienced by approximately half of women with a UTI.[17] The physical consequences of a UTI are a particular problem in elderly patients where UTIs may provoke or aggravate existing incontinence.[18] Patients can also suffer from reductions in mental QoL, with at least two-thirds of patients reporting worse mental health than the general population.[17] The nature of UTI episodes, which are frequently sudden and unpredictable can additionally lead to anxiety, social handicap and depression, the latter of which affects over 60% of women with recurrent UTIs.[16,17]

The impact of recurrent UTIs persists beyond the time of infection, with symptoms of pain and/or burning while urinating, dysuria and pollakiuria being the most commonly persisting symptoms from the previous infection.[16] Consequently, physical and mental health (i.e. increased risk of depression) frequently continue to be lower than the general population in approximately 50% of patients 4 weeks after UTI episode.[17]

As the incidence of antibiotic resistance continues to increase but the number of newly antibiotic agents discovered decreases, treatment options are becoming more limited, exacerbating the impact of UTIs on QoL, in addition to increasing mortality and healthcare costs. Together, this indicates a **need for alternative and tolerable prophylactic options to improve clinical outcomes and QoL, and reduce antibiotic use in patients who experience recurrent UTIs.**[19]

TREATMENT AND PREVENTION OF URINARY TRACT INFECTIONS: WHAT DO GUIDELINES RECOMMEND?

Appropriate short-term antibiotic therapy remains the standard treatment to achieve symptomatic relief of acute symptomatic infections, with symptoms generally resolving within 3 days.

The EAU Guidelines 2020 stress the importance of antimicrobial stewardship to optimize the outcome of prevention and treatment of infection whilst curbing the overuse and misuse of antimicrobial agents.[6] In case of recurrent UTIs, this should include a series of measures to ensure rational and evidence-based use of antimicrobials in their prevention and treatment as well as non-antimicrobial strategies.

The EAU Guidelines recommend a stepwise approach for the prevention of recurrent UTIs in women, starting with counseling and behavioral measures such as increased fluid intake, post-coital urination or better hygiene after defecation.

The second intervention to be considered consists of **non-antimicrobial prophylaxis**. The Guidelines recommend the **use of immunoactive prophylaxis with OM-89 in women with recurrent UTIs, with recommendation "Strong" based on 1A level of evidence**. Vaginal estrogen replacement may be used in postmenopausal women, with a recommendation "Weak", based on 1B level of evidence. No recommendations can be made on other non-antimicrobial preventative options such as cranberry products, probiotics (*Lactobacillus spp.*) and D-mannose, due to insufficient or conflicting clinical evidence.[6]

Antibiotic prophylaxis is recommended only when all non-antimicrobial measures to prevent recurrences have failed. Indeed, although they have shown to be effective in the prevention of recurrent UTIs, the rise of antibiotic resistance, even to new-generation antibiotics, impose to keep this measure only as a last resort. Globally, the incidence of resistance to many antibiotic classes is greater than 20% for the common causative pathogens of recurrent UTIs, rendering many drug classes ineffective.[20] Patients with antibiotic resistant UTIs have increased hospital lengths of stay, healthcare costs and risk of mortality.[21,22] Continuous or post-coital low dose antibiotic prophylaxis has been shown to reduce the rate of recurrent UTIs (recommendation "strong", level of evidence 1b, with patients informed of the potential for adverse effects*).

OM-85 is also recommended in several local guidelines and consensus papers including in Brazil, Germany, Mexico, Russia, and South Korea and Switzerland, along with the Latin American Regional consensus (Figure 1).[23–31]

EAU RECOMMENDATION FOR PROPHYLAXIS OF RECURRENT UTIS AND REDUCTION OF ANTIBIOTIC USE

1. Counselling* and behaviour modifications
*regarding avoidance of risk factors

2. Non-antimicrobial preventive measures

3. Antimicrobial prophylaxis
(only if non-antimicrobial preventive measures are unsuccessful)

EVIDENCE 1a
RECOMMENDATION STRONG

Among non-antimicrobial prophylaxis measures, immunoactive prophylaxis with OM-89 received the highest rating in terms of level of evidence (1a) and strength of recommendation (Strong).

Fig. 1: Local and regional guidelines recommendations for OM-89

Key points

- Uncomplicated UTIs are one of the most common bacterial infections
- Up to 80-90% of all cases occur in women
- Nearly half of women present a least one lower UTI (cystitis) in their lifetime
- 25% of these women will experience UTI recurrence, defined as at least 2 symptomatic infections in 6 months or 3 in 1 year
- The majority of cystitis cases are caused by uropathogenic *E. coli* (UPEC)
- Antibiotics are the mainstay treatment for all UTIs
- The increasing emergence of antimicrobial drug-resistant bacteria is a continuing challenge
- Non-antimicrobial prevention strategies are thus recommended in the EAU guidelines, with antimicrobial prophylaxis considered only when alternative methods have failed
- Among non-antimicrobials, immunoactive prophylaxis with OM-89 has been recommended since 2010 in the EAU Guidelines and is strongly recommended with a 1a level of evidence since the 2019 Guidelines Update
- OM-89 is recommended in local and regional guidelines and consensus papers for the management of recurrent cystitis

* Depending on the type of antibiotic prophylaxis (1b: continuous or post-coital; 2b: self-administrated short term)

Prevention of recurrent UTIs - Introduction on OM-89

Most alternative strategies do not focus on destroying the infective agent, as does antimicrobial therapy, but instead aim at protecting the host from infection. One method to achieve this goal is to prime the patient's mucosal immune system to react promptly against harmful uropathogens by oral administration of an immunostimulant.

OM-89 was first registered in Switzerland in September 1987, and is now available in more than 50 countries. The safety and therapeutic benefits of OM-89 are supported by a large body of clinical trial data. Since its launch, nearly 5.8 million patients have been treated with OM-89.

COMPOSITION AND PRESENTATION

The active component of OM-89 (laboratory code) is a lyophilized powder containing 6 mg per capsule of bacterial lysates derived from 18 selected and standardized *E.coli* strains known to be the most common isolated uro-pathogens responsible for cystitis.[32]

The final product consists mainly of acidic proteins, peptides and amino acids. This product is an orally-administered enhancer of the immune response.[33] Its activity is not limited to the strains used for its manufacture, as it also prevents preventions by other pathogenic micro-organisms, such as *Proteus mirabilis* and *Klebsiella pneumoniae*, and hence confers protection against a wide spectrum of uropathogens.[34,35]

Based on the results of long-term stability studies, the drug product must be stored in controlled room temperature and protected from humidity according to data from the International Conference on Harmonization (ICH), stating conditions of 25°C and 60% relative humidity. Under these conditions, the capsules have a shelf-life of up to 5 years.

CLINICAL INDICATIONS*

OM-89 is indicated in the prevention of recurrent lower UTIs. OM-89 is also indicated for the treatment of acute UTIs, as co-medication to conventional antimicrobial therapy.

DOSAGE AND ADMINISTRATION

OM-89 is administered orally as one capsule daily on an empty stomach for 3 consecutive months (90 days). In Germany, OM-89 booster posology is currently registered. In this perspective, 3 months after discontinuing standard drug therapy, one OM-89 capsule is given daily for the first 10 days of each month for 3 consecutive months. The boosting regimen provides an added benefit to patients compared with the standard posology, meaning that it helps prolong the protection against UTI.

Month 1	Month 2	Month 3	Month 4	Month 5	Month 6
90 days					

* The indication and dose information is based on the Swiss Prescribing Information; this information should be updated based on the local prescribing information.

LIMITATIONS FOR USE

General warnings: In case of cutaneous reactions, fever or occurrence of an edema, the treatment should be interrupted as these may constitute allergic reactions. Immunosuppressive treatments are likely to reduce or block the efficacy of a treatment with OM-89.

Contraindications: Known hypersensitivity to the active ingredients/substance or to any of the excipients.

Precautions: The efficacy and safety of OM-89 have not been established in children below 4 years.

Pregnancy and breastfeeding: There are only minimal data from on use of OM-89 in pregnant women.

One pilot study was conducted in a small group of pregnant women (n= 62) with acute urinary tract infection (UTI) in second trimester of pregnancy until delivery. OM-89 was well tolerated and newborns were healthy with normal Apgar scores.[70] No studies have been performed in women during the first 3 months of pregnancy. Animal studies do not indicate direct or indirect harmful effects with respect to pregnancy, embryonal/fœtal development, parturition or postnatal development. While prescribing OM-89 during the first trimester potential risks should be weighed against benefits and doctor's discretion is advised. As a precautionary measure, it is preferable to avoid the use of OM-89 during pregnancy.

No data are available, OM-89 should only be used during breastfeeding after a thorough risk-benefit assessment.

Interactions: No drug interactions have been reported until now (No data available).

Overdose: No cases of overdose have been reported.

Ability to drive and use machines: There has been no study to date. It is unlikely that OM-89 has an effect on the ability to drive or use machines.

Key points

- OM-89 is indicated
  - for the prevention of recurrent lower urinary tract infections
  - as co-medication to conventional antimicrobials in the treatment of acute urinary tract infections
- OM-89 is given as one capsule daily for 3 consecutive months
- Since its launch, nearly 5.8 million patients have been treated with OM-89

Mechanism of action

OM-89 is an oral immunotherapy, which activates the host's immune defense mechanism via the common mucosal system (mucosal-associated lymphoid tissue = MALT) and maintains these defenses at an effective level. It is an immune-enhancer as it prepares the patient to better respond to an infection by **stimulating both the innate and adaptive immune systems**, thereby increasing the patient's natural defenses against lower UTIs.

CHEMICAL LYSIS

After ingestion, the components of the bacterial extract OM-89 are able to pass through the stomach. Indeed, the antigenic proteins and peptides containing D-amino acids have been chemically modified during a process of chemical lysis which partially preserves only part of their antigenic structures. Therefore, they are still able to stimulate the immune system.[36] Moreover, and from the safety point of view of this product, the alkaline lysis decreases the levels of native lipopolysaccharides (LPS or endotoxins known to be responsible for septic shock) by chemical modification.[37] Alkaline lysis detoxifies the Lipid A moiety of LPS by reducing the total number of fatty acids bound to Lipid A, leading to new immunological properties of the detoxified LPS.

Agonists and antagonists of the toll-like receptors, TLR2 and TLR4, which are present in the extract, are amphiphilic molecules. As a result, these components are absorbed in the ileum and jejunum and reach the Peyer's patches, which are collections of immunocytes located under the intestinal wall.

Peyer's patches contain microfold (M) cells in their epithelia. These M cells, capable of recognizing immunoactive substances, bring the bacterial extracts of OM-89 into contact with antigen-presenting cells (APCs) and prime the immune system (Fig. 2).

HOST INNATE IMMUNITY

When bacterial fractions from OM-89 are recognized as "danger signals", the innate immunity is polarized. As a result, APCs in the Peyer's patches are stimulated, resulting in accelerated maturation of dendritic cells[38] and enhanced phagocytic activity of macrophages and neutrophils[39], as well as an increased expression of adhesion molecules at the neutrophil surface.[40] While sensing of the mucosal surface by OM-89 is taking place, stimulated APCs will also migrate via the lymphatic system and blood vessels to the mucosa-associated lymphoid tissue (MALT), including of the urinary tract. There, they provide local immunoprotection by stimulating the proliferation and activity of B cells and the secretion of polyclonal high and low-affinity immunoglobulin A (sIgA) molecules via a T-cell-dependant pathway.[41, 42]

In the peripheral blood, the production of tumor necrosis factor α (TNF-α), interleukin-6 (IL-6), IL-10[43], IL-12,[43] and interferon-γ (IFN- γ)[44] by monocytes is induced.

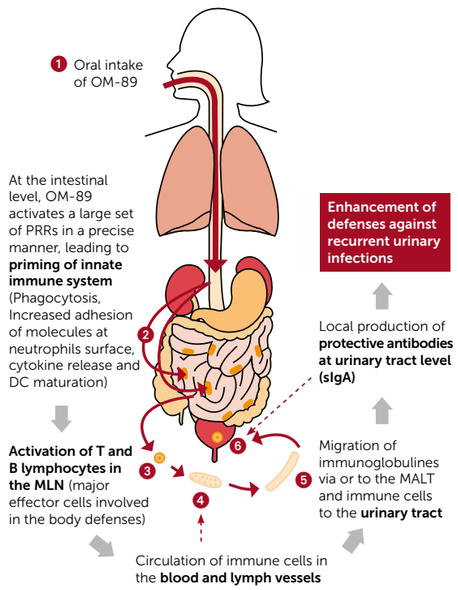


Fig. 2: Proposed mechanism of action of OM-89

HOST ADAPTIVE IMMUNITY

Host adaptive immunity is also induced by OM-89 via the activation of T helper cells by APCs in the mesenteric lymph nodes. Of these, T cell polarization and Th1 response including the secretion of various types of immunoglobulins in a T-cell dependent mechanism.[40,41]

This polyclonal humoral response is then capable to prepare cells to respond to most pathogens that would be re-exposed to the immune system.

The proposed mechanism of action of OM-89 is supported by several *in vitro* and *in vivo* experiments.

OM-89 *IN VITRO* EFFECTS

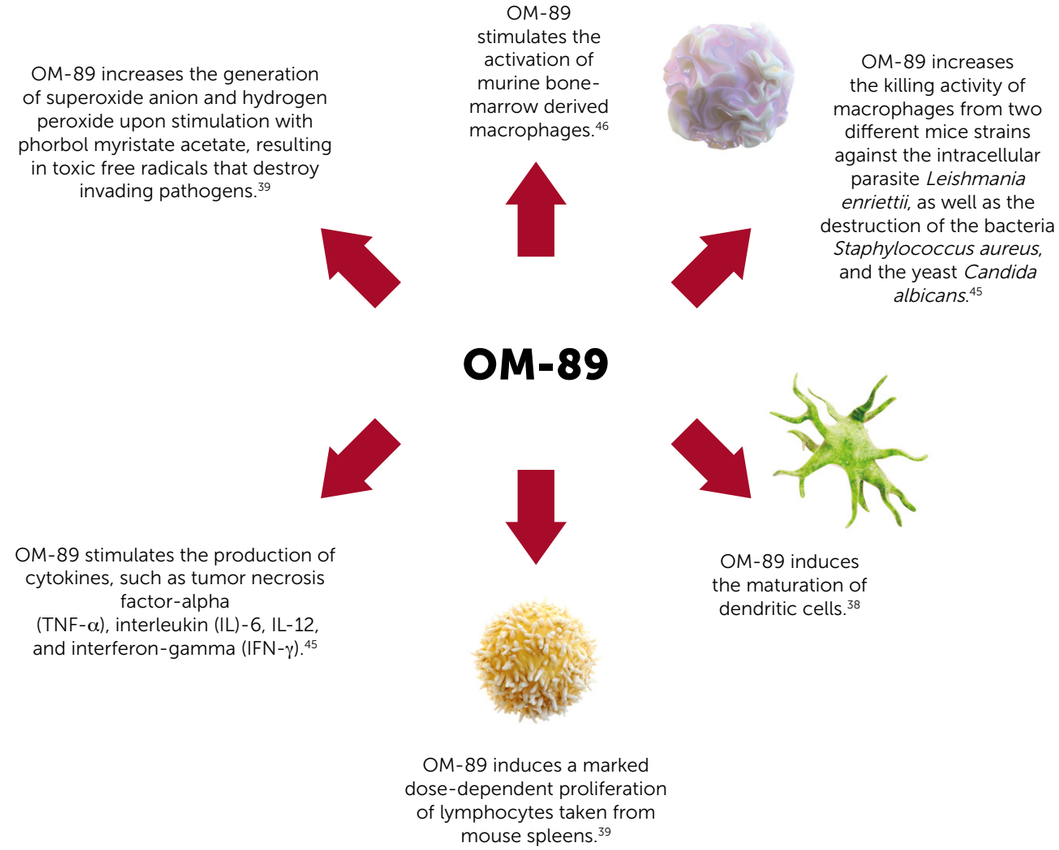


Fig. 3: OM-89 *in vitro* effects

PRR; Pattern-recognition receptors. **MLN**; Mesenteric lymph nodes

OM-89 *IN VIVO* EFFECTS

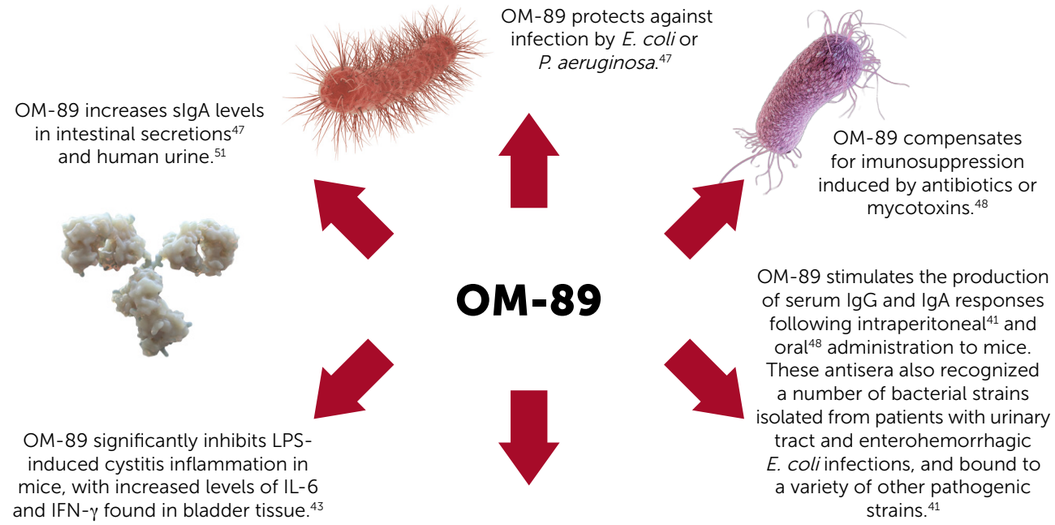


Fig. 4: OM-89 *in vivo* effects

Key points

- The components of the bacterial extract OM-89 are modified due to the chemical lysis which partially preserves their key antigenic determinants.
- They are absorbed in the jejunum and ileum, where antigen-presenting cells in the Peyer's patches are activated.
- As a result, the maturation of dendritic cells is increased, phagocytic activity of macrophages enhanced, expression of adhesion molecules at the neutrophilic surface elevated, and production of cytokines by macrophages induced.
- B and T lymphocytes are stimulated and migrate via blood and lymph vessels to mucosal-associated lymphoid tissues (MALTs), including urogenital tract mucosa-associated lymphoid tissue.
- Stimulated lymphocytes provide local immunoprotection by secreting immunoglobulin A (sIgA) molecules able to recognize some ingested bacterial fragments contained in OM-89.
- Different bacteria contain common PAMPs, similar to the ones included in the composition of OM-89, thus inducing a broad non-specific pre-alert state against uropathogens. In this manner, OM-89 confers protection against bacterial pathogens commonly involved in UTIs, regardless of pathogen.
- OM-89 has been evaluated for its anti-inflammatory effect in a model of LPS-induced cystitis in mice.
- On-going pre-clinical studies will provide further insights on potential immunoregulatory properties of OM-89.
- In conclusion, OM-89 enables the patient to better respond to an infection by stimulating both the innate and adaptive immune systems and regulating inflammation, resulting in an enhancement of the patient's defenses against recurrent UTIs.

Key Clinical Evidence

Several placebo-controlled, double-blind studies in otherwise healthy premenopausal and postmenopausal women from 17 to 72 years of age with recurrent UTIs, in addition to studies performed in specific populations (patients with neurogenic bladder dysfunction) and a number of open-label trials[52-54] have been published, confirming its efficacy and safety and the clinical relevance of the aforementioned immunological findings. The longer-term effects of OM-89 (including one double-blind study) as well as the effects of booster dosage were also investigated. A few pilot open-label studies were conducted in children, pregnant, and exclusively in postmenopausal women. A brief summary of the most relevant studies, along with information on the dosing regimen, number of patients treated, duration of follow-up, and study design is provided in Table 3 below.

Table 3

Study, year	Dosing regimen	Patients enrolled	Study duration	Study design
Efficacy under conventional dosing scheme of 90 days				
Frey *et al.* 1986	90 days	n=64	6 months	DBPC*
Tammen *et al.* 1988	90 days	n=521	6 months	open
Schulman *et al.* 1993	90 days	n=166	6 months	DBPC
Magasi *et al.* 1994	90 days	n=122	6 months	DBPC
Loran *et al.* 2015	dosage used in routine clinical practice	n=52	6 months	observational
Long-term efficacy				
Tammen *et al.* 1990	90 days	n=150	6-11 months	DBPC
Efficacy under booster dosage				
Rugendorff *et al.* 1992	90 days, 3 month break, 10 days/ month for 3 months	n=89	Retrospective 24-month evaluation**	open
Bauer *et al.* 2005	90 days, 3 month break, 10 days/ month for 3 months	n=453	12 months	DBPC
Popa *et al.* 1996	90 days, 3 month break, 10 days/ month for 3 months	58 postmenopausal women	See Note***	open
Efficacy in special patient populations				
Hachen 1990	90 days	70 spinal cord injury patients	6 months	DBPC
Krebs *et al.* 2018	90 days, 3 month break, 10 days/ month for 3 months	136 patients with spinal cord injury	12 months	Retrospective cohort
Wade *et al.* 2020	90 days	49 patients with neurogenic bladder dysfunction (incl. spinal cord injury)	6 months	DBPC
Baertschi *et al.* 2003	6 mg/day until delivery	70 pregnant women	3-6 months + 6 weeks after delivery	open
Lettgen 1996	6 mg/day for 6 months	40 children	18 months	open
Czerwionka-Szaflarska *et al.* 1996	90 days	38 children	6 months	open
Systematic review and meta-analysis				
Bauer *et al.* 2002	90 days	n=601	6 months	5 DBPC
Naber *et al.* 2009	90 days	n=975	6-12 months	5 DBPC
Beerepoot *et al.* 2013§	90 days - 9 months	n=891	6-12 months	4 DBPC
Neho *et al.* 2016	90 days - 9 months	n=788	6-12 months	5 DBPC
Aziminia *et al.* 2019§	90 days - 9 months	n=1,148	6-12 months	6 DBPC

*DBPC: double-blind, placebo-controlled study
**Retrospective evaluation with follow-up up to 24 months after the start of OM-89 therapy
***Note: each patient was monitored for 9 months after the start of OM-89 therapy
§Only OM-89 study information is shown here; the meta-analysis also included other methods of non-antibiotic prophylaxis which are not included in this summary table.

EFFICACY UNDER CONVENTIONAL DOSING SCHEME OF 90 DAYS

Frey et al.[55] 1986
Treatment of recurrent urinary tract infections: efficacy of an orally administered biological response modifier. Urologia Internationalis

This 6-month, double-blind, placebo-controlled, multicenter study evaluated the efficacy of OM-89 in reducing UTIs, antibiotic consumption, and clinical symptoms.

Population
A total of 64 patients, mostly women suffering from recurrent lower UTIs, were enrolled: 32 were given OM-89 and 32 received placebo.

Parameters and treatment modalities
- Patients were given one daily capsule of OM-89 (6mg/day) or placebo for 3 months, followed by a 3-month wash-out period.
- Examinations for bacteriuria (number of UTIs defined as $\geq 10^4$ bacteria/ml), dysuria, and leukocyturia were performed at baseline, 1 week after the end of the initial antibiotic treatment, and at 3 and 6 months. Duration of concomitant antibiotic treatment was recorded.

Results
- Significant reduction in the percentage of patients with bacteriuria at 3 and 6 months (Table 4).
- Significant reduction in the percentage of patients with leukocyturia and dysuria at 6 months (Table 4).
- The duration of concomitant antibiotic prescription was significantly lower (-78% in the OM-89 group) than in the placebo group (2.7±5.9 days vs. 12.1±16.9 days, p<0.01).
- **Regarding safety data, only one adverse event (1.6%) was reported in the OM-89 group (exanthema).**

Table 4: Evolution of urinary parameters and symptoms.[55]

Evolution of urinary parameters and symptoms (% of patients)								
Parameter	**Baseline**		**Week 3-4**		**Month 3**		**Month 6**	
	Placebo	**OM-89**	Placebo	**OM-89**	Placebo	**OM-89**	Placebo	**OM-89**
$\geq 10^4$ total bacteria/ml	100	100	27	25	48	16[1]	39	19[2]
≥5 leukocytes/field	94	91	32	36	38	16	39	12[2]
Dysuria	84	82	14	15	15	0	24	0[2]

[1] p<0.01; [2] p<0.05

Conclusions

OM-89 significantly improved both the laboratory and clinical parameters associated with UTIs.

Tammen and Frey[58] 1988
Treatment of recurrent urinary tract infections with OM-89. Urologe B

This 6-month open multicenter trial was aimed at evaluating OM-89 in a large patient population under clinical practice conditions.

Population
A total of 521 patients (81% female) with frequent UTI recurrences were enlisted in 23 German and 67 Swiss practices, with 451 being included in the final analysis.

Parameters and treatment modalities
- Patients received OM-89 (6mg/day) for 3 months, with a 3-month follow-up period.
- The main clinical evaluation criteria was the number of recurrent UTIs ($\geq 10^5$ bacteria/ml in midstream urine).
- Other parameters included gram-negative counts, incidences of dysuria and pollakiuria, and duration of concomitant antibiotic/chemotherapeutic administration.

Results
- Following OM-89 administration, a significant reduction in the mean number of recurrences compared to the preceding 6 months was observed, from 3.6 to 0.85/patient (p<0.001).
- Total bacterial counts were significantly reduced at all times versus baseline (p<0.001).
- The incidences of dysuria and pollakiuria were significantly reduced (p<0.01) (Fig. 7).
- The consumption of antibiotics/chemotherapeutics was markedly reduced.
- **OM-89 was well tolerated, with 23 out of 521 patients (4.4%) reporting side effects: gastrointestinal troubles (n=15), headaches/vertigo (n=3), pruritus (n=3), nausea and erythema (n=1), and hair growth interruption (n=1). Only two patients withdrew from the study due to gastrointestinal troubles and nausea and erythema.**

Clinical symptoms

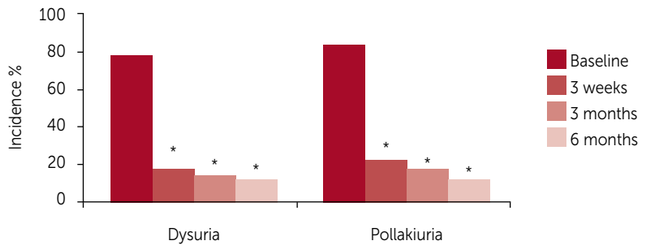


Fig. 7: Incidences of dysuria and pollakiuria before, during, and after treatment with OM-89
*p<0.01
Adapted from Tammen and Frey (1988).

Conclusions

The use of OM-89 significantly reduced the number of UTI recurrences, symptom severity and the need for antibiotics, when compared to before the start of the study. The study results demonstrated the usefulness of OM-89 in reducing the risk of further symptomatic recurrences of UTIs. Its use was well tolerated when used in clinical practice on a relatively big group of patients.

Schulman et al.[56] 1993
Oral immunotherapy of recurrent urinary tract infections: a double-blind placebo-controlled multicenter study. The Journal of Urology

This 6-month double-blind multicenter study compared the efficacy of OM-89 versus placebo in adult patients with recurrent UTIs.

Population
- 166 eligible patients were recruited, with 160 (45.3±2.0 years; 84% female) included in the final analysis, 82 of which were given OM-89 and 78 placebo.
- Inclusion criteria were adults with symptomatic recurrent UTIs in the acute phase with frequent past recurrences (at least two per year). The infection had to be characterized by $\geq 10^5$ bacteria/ml in a midstream urine specimen or $\geq 10^4$ bacteria/ml in a catheterized urine sample.

Parameters and treatment modalities
- Patients received OM-89 (6mg/day) or placebo for 3 months, with a 3-month follow-up period.
- Main clinical evaluation criteria were number of recurrent UTIs (based on bacteriuria) and consumption of antibiotics/ chemotherapeutics.
- Other parameters included laboratory parameters (leukocyturia, erythrocyturia, albuminuria, *etc.*) and presence of dysuria.

Results
- Bacteriuria recurrences ($\geq 10^5$ bacteria/ml in midstream urine) were significantly lower (-49%) in the OM-89 group.
- In addition, bacteriuria recurrences ($\geq 10^4$ bacteria/ml in midstream urine) were significantly lower (-36%) in the OM-89 group (Fig.5).
- A significant ($p \leq 0.03$) decrease (-36%) in antibiotics/chemotherapeutic consumption*, which was even more marked (-67%, $p<0.002$) during the second half of the study was observed in the OM-89 group (Fig.6).
- **Regarding safety, two adverse events were observed in the OM-89 group, notably vertigo with visual troubles (possibly related) and subcutaneous nodules (unrelated), versus 11 in the placebo group.**

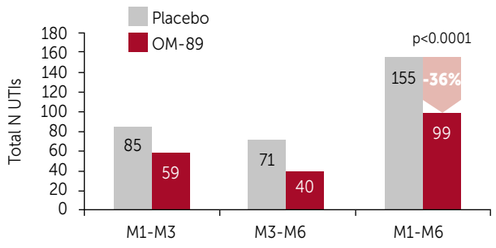


Fig. 5: Number of recurrent UTIs in the OM-89 and placebo groups [56]

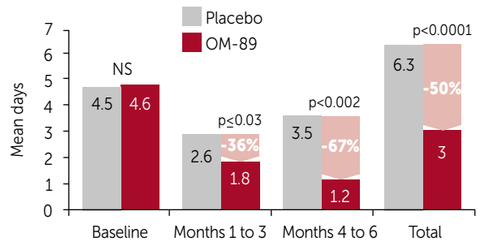


Fig. 6: Consumption of antibiotics in the OM-89 and placebo groups [56]

From Schulman 1993. Used with permission.
* Mostly cotrimoxazole and broad-spectrum penicillins.

Conclusions

OM-89 may be considered an efficient preventive treatment of recurrent lower UTIs and their accompanying signs and symptoms, as it was shown to decrease the risk of recurrence and need for antibiotic/antibacterial agents. The protective effect was still present 3 months after stopping OM-89 administration.

Magasi et al.[57] 1994
OM-89 and the management of recurrent urinary tract infection in adults: a randomized multicenter double-blind trial. European Urology

This 6-month double-blind multicenter study investigated the frequency of recurrences under OM-89 versus placebo in adult patients using a double-blind study design.

Population
122 patients with recurrent UTIs were recruited, with 112 (87% female) being included in the final analysis: 58 were given OM-89 and 54 placebo.

Parameters and treatment modalities
- Patients received OM-89 (6mg/day) or placebo for 3 months, with a 3-month follow-up period. The main clinical evaluation criteria was the number of recurrent UTIs ($\geq 10^5$ bacteria/ml in midstream urine). Other parameters included incidences of bacteriuria, dysuria, and leukocyturia.

Results
- A significantly lower number of UTI recurrences was found in the OM-89 group compared to the placebo group (13.8% *vs.* 79.6%; $p<0.0005$).
- 67.2% of OM-89 patients had no recurrence during the study compared to 22.2% in the placebo group ($p<0.0005$). Significantly lower incidences of bacteriuria (-86%), dysuria (-82%), and leukocyturia (-58%) in the OM-89 group were seen compared to the placebo group (Table 5).
- **OM-89 was well tolerated, with no reported side effects.**

Table 5: Incidences of bacteriuria, dysuria, and leukocyturia during the study period.[57]

Incidences of bacteriuria ($\geq 10^5$ germs/ml), dysuria, and leukocyturia during the study period (%)						
Parameter	**Baseline**		**After 3 months**		**After 6 months**	
	Placebo	**OM-89**	Placebo	**OM-89**	Placebo	**OM-89**
Bacteriuria	100	96.5	55.5	**10.3**[1]	24.1	**3.4**[2]
Dysuria	90.7	96.5	ND	ND	18.5	**3.4**[3]
Leukocyturia	96.7	86.2	ND	ND	37.0	**15.5**[3]

[1] $p<0.0005$; [2] $p<0.001$; [3] $p<0.005$; ND=Not done

Conclusions

A 3-month course of OM-89 significantly reduces the number of UTI recurrences as well as the incidence of bacteriuria, dysuria, and leukocyturia. The protective effects were still evident 3 months after discontinuing therapy.

Loran O.B. et al.[59] 2015
Rational therapy for recurrent infections of the lower urinary tract. The results of a prospective observational program to assess the effectiveness and safety of Ceforal®*, Solutab®* and OM-89 in patients with recurrent uncomplicated lower urinary tract infections (FLORA).

This prospective observational program aimed at assessing, in routine clinical practice, the efficacy and safety of the combination of an antibiotic used to treat cystitis in the acute phase, concomitantly with OM-89 in the prevention of future episodes of recurrent uncomplicated urinary tract infections.

Population
52 women completed the 5 visits (Day 0, 10, 30, 90 and 180) to the doctor within the 6 months duration of the observational program.

Parameters and treatment modalities
- Primary endpoint: Assessment of the number of recurrent episodes of acute UTI over 6 months.
- Secondary end point: Assessment of the duration of recurrent episodes of acute UTI and frequency of adverse side effects over 6 months.
- Baseline characteristics: The average age of the patients was 42.4±16.2 years and the average duration of the disease (cystitis) was 1.1±2.6 years.
- Start of combined antibiotic + OM-89 therapy at the 1st visit during the acute phase of a cystitis episode.

Results
- 6 months after inclusion in the program, the average number of acute episodes significantly decreased from 2.8 infections (before treatment) to 0.2 (p<0.001) (Fig. 8)
- The average duration of acute episodes was significantly reduced, from 8.7 to 0.5 days (p<0.001) after 6 months of treatment compared to the 6 months period before the program (Fig. 9)
- Parallel to the reduction in number and duration of UTI recurrences, a 90% reduction in the mean duration of antibiotic consumption was observed after 6 months of inclusion in the program (p<0.001) (Fig. 10)

Fig. 8: Average number of acute episodes of UTI over 6-months period before and after treatment.[59]

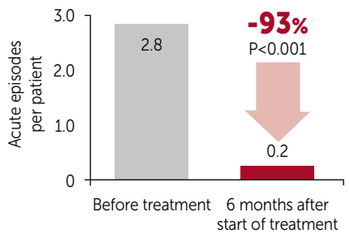


Fig. 9: Average duration of acute episodes of UTI over 6-months period before and after treatment.[59]

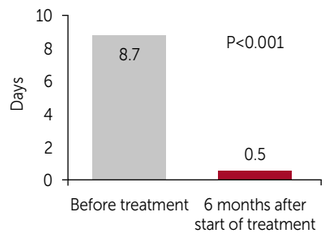
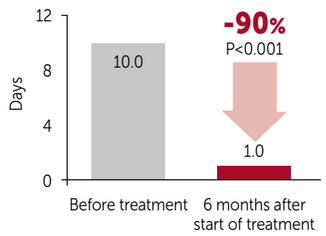


Fig. 10: Average duration of antibiotic therapy per patient during a 6-month period before and after treatment (in days).[59]



Conclusions

Compared to before study treatment, the use of OM-89 initiated concomitantly to an antibiotic during the acute episode of cystitis has been shown to:
- significantly reduce the number and duration of recurrent UTI
- significantly reduce antibiotic consumption
- be well tolerated (none of the participants experienced adverse side effects), suggesting that OM-89 can be safely initiated concomitantly to antibiotics during an acute infection

Key points

- As treatment regimen for recurrent cystitis, initiation of OM-89 during the acute phase, concomitantly to an antibiotic, is effective in preventing recurrent UTIs and is well tolerated. This prospective open label study supported the tolerability of the product and its efficacy as shown in randomized clinical trials. The percentage of reduction of the pre-defined endpoints are vs prior to the study and are herefore not comparable with the reductions observed in RCT.

*Ceforal Solutab = cefixime (third-generation cephalosporin)

LONG-TERM EFFICACY

Tammen et al.[60] 1990
Immunobiotherapy with OM-89 in recurrent urinary tract infection. British Journal of Urology

The aim of this double-blind, placebo-controlled study was to assess the efficacy of OM-89 in comparison with placebo.

Population
150 patients with recurrent UTI were enrolled, with 120 (85% female) included in the final analysis, 61 of which received OM-89 and 59 placebo. Fifty-seven patients were further observed for a 5-month period.

Parameters and treatment modalities
- Patients received OM-89 (6mg/day) for 3 months, with a 3-month follow-up period, which was prolonged for another 5 months in 57 patients.
- The number of recurrent UTIs ($\geq 10^4$ bacteria/ml in midstream urine) was assessed.
- Main clinical evaluation criteria were the mean number and total number of UTIs, as well as the distribution of patients according to the number of recurrences.
- Other parameters included incidences of bacteriuria, dysuria, and nitrituria, as well as duration of antibiotic/chemotherapeutic use.

Results
- There was a significant reduction in the mean number of recurrences in the OM-89 group: 0.82 vs. 1.8 (-58%) recurrences in the placebo group ($p<0.001$) during the first 6 month period.
- 37.7% of the OM-89 patients had no recurrences during the study compared to 17% in the placebo group ($p<0.001$; Fig. 11).
- The distribution of patients according to the number of recurrences during the 6-month trial period (Fig. 11). Bacteruria, dysuria, nitrituria, and antibiotic use were significantly decreased by OM-89 *vs.* placebo.
- During the additional 5-month follow-up, there were fewer UTI in the OM-89 group compared to placebo (37% [10/27] versus 67% [20/30] respectively, $P<0.05$; Fig. 12).
- Antibiotics consumption was similar in the two groups during the first 3 months of the trial. However, for the overall 6 month trial period, it was significantly less in the OM-89 group ($p<0.001$).
- **Side effects possibly related to OM-89 were observed in four patients (5.4%): pruritus, diarrhea, headache with flushing, and allergic reaction. This last reported side effect led to patient withdrawal from the study.**

Fig. 11: Distribution of patients according to the number of recurrences during the 6-month trial period.[60]

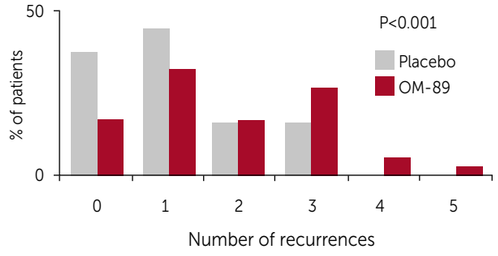
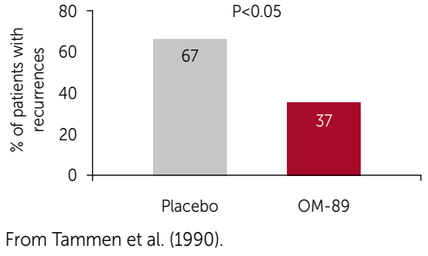


Fig. 12: Recurrences of UTIs in the OM-89 versus placebo groups during the additional 5-month follow-up period.[60]



From Tammen et al. (1990).

Conclusions

The beneficial preventive effects of OM-89 were still present 8 months after discontinuing therapy.

EFFICACY UNDER BOOSTER DOSAGE

Rationale for using the booster dosage

- The susceptibility of the urinary tract to bacterial colonization is attributed to a local immune defect, as reflected by decreased amounts of sIgA. These antibodies secreted into the mucus play a key defense role in mucosal surfaces by preventing the binding between the adhesins synthesized by microorganisms and the corresponding receptors of the epithelial cells. As a result, the adherence, motility, and growth of the bacteria combined with sIgA are impaired,[61] and low sIgA levels are currently considered as a major risk factor for UTI recurrences.

- In animal experiments, OM-89 was shown to offer protection against ascending UTIs by increasing sIgA levels.[62] Accordingly, in the previously summarized clinical studies, OM-89 led to a marked decrease in recurrences of lower UTIs. This protective effect, however, gradually wears off a few months after the last administration of OM-89. A possible explanation for this is that the immunologic memory is transient in this case. It has been hypothesized that, following treatment of the acute episode and the initial 3-month immunoactive prophylaxis, the immune defense should be periodically boosted during the infection-free interval.

- However, exposing the immune system to a long-term stimulation has been thought to be unfavorable, as this may lead to tolerance. For this reason, a therapy-free interval of 3 months was implemented after the initial 3-month OM-89 therapy. Therefore, in the studies evaluating the effects of booster doses, intermittent booster treatment was only initiated following a 3-month drug-free interval.

- The booster dosage regimen is registered in Germany onlywhere the clinical trials with booster regimen were performed.

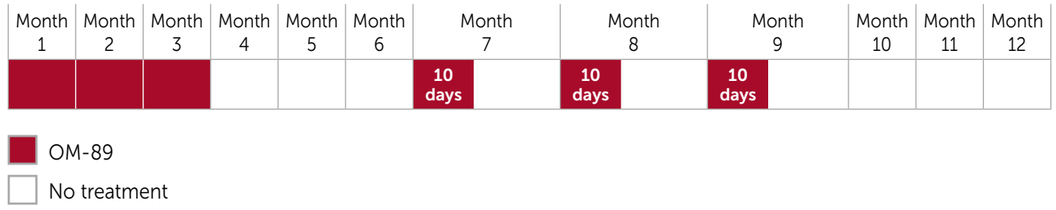


Fig. 13: Booster dosage treatment regimen.

Rugendorff [63] 1992

Immunological therapy of recurrent urinary tract infections with immunoactive E. coli fractions in women. The International Urogynecology Journal

This open, retrospective study evaluated the effects of booster doses of OM-89.

Population
89 female patients, 74 suffering from lower and 15 from upper UTIs were enrolled, with 18 receiving OM-89 booster doses 3 months after initial therapy cessation.

Parameters and treatment modalities
- Patients received OM-89 (6mg/day) for 3 months, with a follow-up of at least 6 months in all 89 patients after the start of immunoactive prophylaxis, and over 12 months in 77 patients. Fourteen patients were observed for over 24 months.
- Booster OM-89 doses were given to 18 patients, 3 months after the end of the initial course, once daily for 10 days per month during 3 consecutive months.
- Target parameters recorded at each visit: number of recurrences, subjective symptoms (*i.e.*, pain, dysuria, frequency, and urgency), leukocyturia, urinary bacterial count, and duration of antibacterial treatment.

Results
- In patients with upper UTI (n=15), the mean number of recurrences fell from baseline, remaining steady during the remainder of the study period (Fig. 14).
- In patients with lower UTI (n=74) who did not receive booster doses (n=56), the number of recurrences was lower during the first 12 months compared to baseline and then gradually increased from month 13 to month 24, but remained lower than in the pretreatment period (Fig. 14).
- In patients with lower UTI who received booster doses (n=18), UTI recurrence rates were statistically significantly lower compared to those without booster doses (p<0.01) (Fig. 14).
- Bacterial counts and antibiotic treatments followed similar patterns to recurrence rates.
- Only two patients (2%) reported side effects, being slight gastrointestinal problems.

Upper and lower urinary tract infection (UTI) recurrences

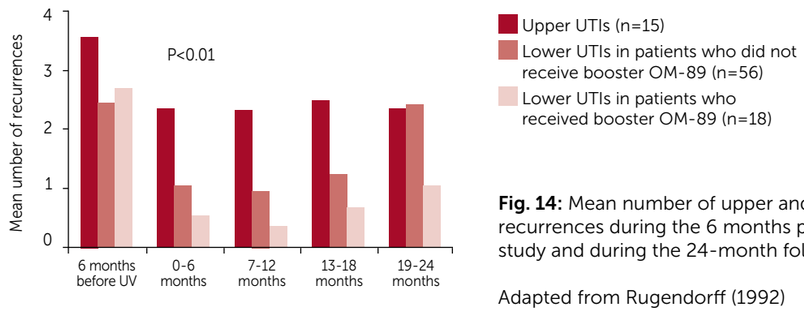


Fig. 14: Mean number of upper and lower UTI recurrences during the 6 months prior to the study and during the 24-month follow-up [63]

Adapted from Rugendorff (1992)

Conclusions

Booster doses of OM-89, given 10 days per month and starting 3 months after therapy cessation, prolonged the preventive action of OM-89.

Bauer et al.[64] 2005

A long-term, multicenter, double-blind study of an Escherichia coli extract (OM-89) in female patients with recurrent urinary tract infections. European Urology

This 12-month, double-blind, placebo-controlled study was designed to investigate the long-term preventive effects of OM-89 in female patients with recurrent UTIs.

Population
453 female patients with ≥3 UTIs in the previous 12 months were enrolled, with 231 receiving OM-89 and 222 placebo.

Parameters and treatment modalities
- Patients received OM-89 (6mg/day) or placebo during Months 1-3, no treatment in Months 4-6, one capsule daily for the first 10 days of Months 7-9, and no treatment in Months 10-12.
- Six visits were scheduled: baseline (Day 0), four control visits (Days 30, 90, 180, and 270), and a final visit (Day 360).
- Primary outcome measures were the rate of acute UTI during 12 months, distribution of UTI per patient, and proportion of patients with at least one post-baseline UTI.
- Secondary measures were the intensity of symptoms and duration of acute UTIs, the frequency of anti-infective prescriptions, and global efficacy assessment by both investigators and patients.

Results
- The mean rate of UTIs over the 12-month study period was significantly reduced by 34% in the active treatment *vs.* placebo group in the ITT analysis (0.84 vs. 1.28; p<0.003) (Fig. 15).

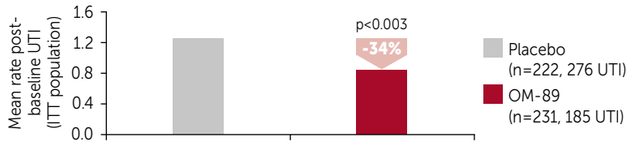


Fig. 15: Reduction in mean rate of UTIs with OM-89 vs. placebo at 12 months (ITT population)[64]

Adapted from Bauer et al. (2005)

- When splitting these results between the first and last 6 months of treatment, a 20% reduction was seen in the first 6 months and a 43% reduction was seen after the booster.
- The distribution of UTIs per patient showed a significant group difference, with 185 recurrences in the OM-89 versus 276 in the placebo groups (p<0.002) (Fig. 16).

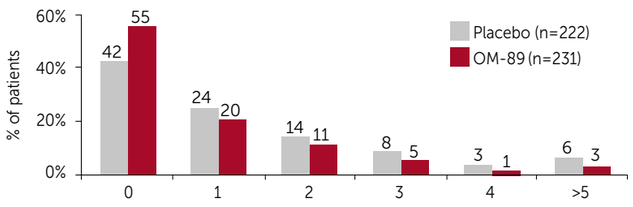


Fig. 16: Distribution of post-baseline UTI recurrences per patient (p<0.002)[64]

Adapted from Bauer et al. (2005)

- The average number of anti-infective prescriptions was significantly (p=0.005) lower in the active group versus placebo group (2.44± 1.75 vs. 2.79± 2.07, respectively, corresponding to a 13% reduction).
- **A total of 161 adverse events affected 75 patients in the active group compared to 192 in 71 patients in the placebo group during the course of this clinical trial, with 13% being considered to be related to treatment in both groups.**

Conclusions

- This key double-blind, placebo-controlled study confirmed the protective effects of OM-89 during the 12-month study period, which included 3 months of treatment and three 10-day booster courses over a further 3-month period. It desmontrated the added and prolonged benefit of the boosting regime.
- The study findings further support the rationale for using OM-89 booster dosages.

Popa et al.[65] 1996

Recurrent postmenopausal urinary tract infections. Efficacy of oral immunotherapy with E. coli fractions. Münchener Medizinische Wochenschrift

This open observational study was carried out in three urological practices in Germany in order to collect data on the effects of OM-89 in postmenopausal women.

Population

A total of 58 (55 evaluable) postmenopausal women, with an average age of 66 years, with recurrent uncomplicated UTIs were enrolled.

Parameters and treatment modalities

- Patients received OM-89 (6 mg/day) for 3 months, followed by a 3-month interval intermission, after which booster doses of OM-89 were given on 10 consecutive days each month for 3 months.
- Each patient was monitored for about 9 months.

Results

A 65% reduction in the mean UTI recurrence rate was observed in the 55 evaluable patients during the study period (Fig. 17).

Urinary tract infection (UTI) recurrences

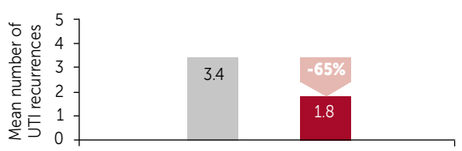


Fig. 17: Mean incidence of UTI recurrences during the 6 months preceding the study compared to the 9-month study period[65]

Adapted from Popa et al. (1996)

Conclusions

In postmenopausal women with recurrent uncomplicated UTIs, treatment with OM-89 seems to achieve a similarly high protection as in younger female patients.

SPECIAL PATIENT POPULATIONS

The efficacy and safety of OM-89 was also evaluated in special patient populations, in several clinical studies including spinal cord injury patients, pregnant women and children.

Hachen et al.[68] 1990
Oral immunotherapy in paraplegic patients with chronic urinary tract infections: a double-blind, placebo-controlled trial. Journal of Urology

The aim of this 6-month double-blind, placebo-controlled crossover trial was to examine the efficacy of OM-89 in spinal cord injury patients with UTIs.

Population
64 spinal cord injury patients with catheter were randomly divided into two groups.

Parameters and treatment modalities
- Patients received either OM-89 (6 mg/day) or placebo for 3 months (phase I), followed by the alternative treatment for another 3 months (phase II).
- Clinical status, urine cultures, and antibiotic consumption were assessed each month.

Results
- There was a marked decrease in bacteriuria during the 1st month in the OM-89/placebo group, which remained for the next 2 months, dropping even lower during phase II as a result of a carry-over effect (no wash-out was planned between the two periods) (Fig. 18).
- In the placebo/OM-89 group, bacteriuria dropped initially in response to antibiotic therapy, but rose again to a significantly higher level than that of the OM-89-treated patients. After switching to OM-89, bacteriuria fell to the level found in the OM-89/placebo group (Fig. 18).

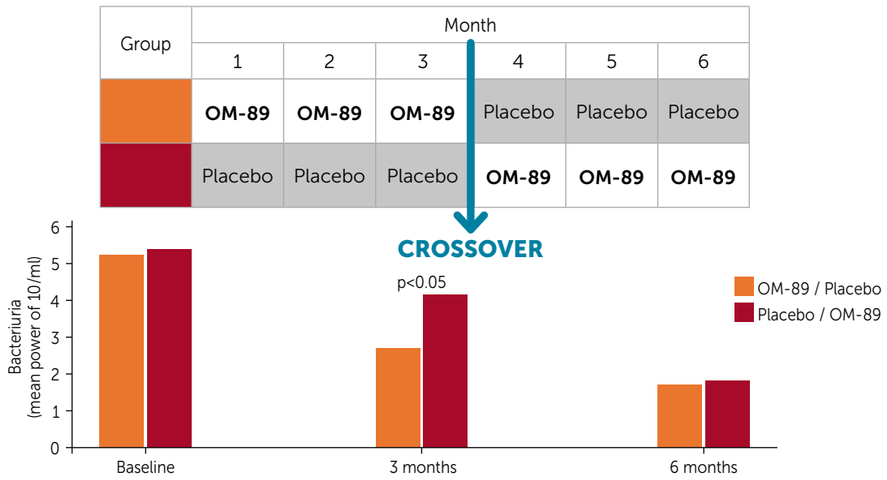


Fig. 18: Evolution of bacteriuria in both patient groups during the 6-month trial

Conclusions

OM-89 offers new therapeutic possibilities in paraplegic patients with severe chronic UTIs.

Krebs et al.[69] 2018
Immunoactive Effects of oral immunomodulation therapy on urinary tract infections in individuals with chronic spinal cord injury — A retrospective cohort study. Neurourology and Urodynamics

This retrospective cohort study tested the hypothesis that oral immunomodulation therapy with OM-89 decreases the frequency of UTIs in patients with spinal cord injury.

Population
136 patients with chronic (> 12 months) neurogenic lower urinary tract dysfunction from spinal cord injury.

Parameters and treatment modalities
- Patients received OM-89 for 3 months, followed by a 3-month interval intermission, after which booster doses of OM-89 were given on 10 consecutive days each month for 3 months.
- Endpoints: proportion of patients with recurrent UTIs in the overall population and subgroups.
- Changes in the frequency of UTIs (none, sporadic [1-2/year] and recurrent [≥3/year] before and after OM-89 were calculated using the Test of Marginal Homogeneity.
- Differences between patient subgroups were determined using Fisher's exact test.

Results
- The proportion of patients with recurrent UTIs decreased significantly (p<0.0001) from 93.4% before treatment to 59.6% with OM-89 (Fig. 19).
- The proportion of patients with no UTIs significantly (p<0.0001) increased from 2.2% before treatment to 20.6% with OM-89 (Fig. 19).
- A significant decrease in the proportion of patients with recurrent UTIs and a significant increase in the proportion of patients with no UTIs with OM-89 was observed in all subgroups stratifications including age (>60 [p=0.003] or ≤60 [p<0.0001] years), injury duration (≥30 [p=0.0006] or <30 [(p<0.0001] years), catheter use (yes or no, both p<0.0001), *E.coli* infection (yes [p<0.0001] or no [p=0.011]), antibiotic use (yes or no, both p<0.0001) and concurrent prophylaxis use (yes or no, both p<0.0001).

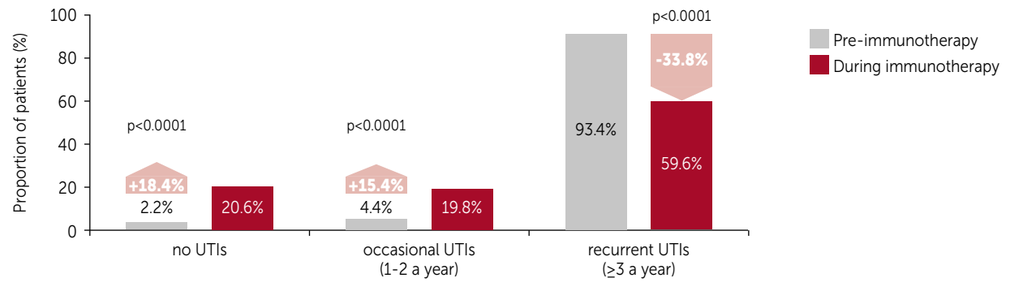


Fig. 19: Proportion of patients with recurrent, sporadic and no UTIs before and with OM-89 treatment

From Krebs et al. 2018.

Conclusions

Oral immunotherapy with OM-89 results in significant and clinically-relevant decreases in UTI frequency in patients with spinal cord injury, regardless of patient age, duration of injury, catheter use and bacterial species involved in UTI.

Wade et al.[70] 2020

Immunotherapy to reduce frequency of urinary tract infections in people with neurogenic bladder dysfunction; a pilot randomised, placebo-controlled trial. Clinical Rehabilitation

This double-blind, randomised, placebo-controlled study evaluated the feasibility for OM-89 in reducing the frequency of urinary tract infections in patients with neurogenic bladder dysfunction.

Population

- A total of 49 patients (mean age 48-50 years in both groups) were included into the study, 23 being randomized into the placebo group, and 25 into the active group.
- Inclusion criteria consisted of patients with a spinal cord injury, multiple sclerosis, transverse myelitis or cauda equine syndrome who had suffered three or more clinically diagnosed urinary tract infections treated with antibiotics over the preceding 12 months.

Treatment and assessment

- All participants took one capsule of oral OM-89 immunoprophylaxis (6 mg) or matching placebo, once daily in the morning for 3 months.
- The primary endpoint was occurrence of a symptomatic urinary tract infection treated with an antibiotic, assessed at 3 and 6 months. Feasibility measures included recruitment, retention and practical difficulties.

Results

- Over 6 months, 18/25 treatment group patients had 55 infections, and 18/23 control group patients had 47 infections. There was not statistically significant difference between the two groups.
- Safety profile was similar in both groups, with no statistically significant differences.

Conclusions

- Based on the study findings, the authors concluded that it is feasible to perform a randomised placebo-controlled trial to assess the efficacy of OM-89 in reducing the rate of recurrent urinary tract infections in patients with neurogenic bladder dysfunction.
- Study results were consistent with previous research and support undertaking a fully powered study involving 350 participants.

Baertschi et al.[71] 2003

Bacterial extract for the prevention of recurrent urinary tract infections in pregnant women: a pilot study. International Journal of Immunotherapy

This open pilot study was aimed at assessing the efficacy of OM-89 in preventing recurrent UTIs in pregnant women.

Population

A total of 62 pregnant women, presenting with an acute UTI in weeks 16 to 28 of pregnancy, were enrolled.

Parameters and treatment modalities

Patients received one capsule of OM-89 (6 mg/day) daily until delivery.

Results

- The incidence of UTI recurrences was significantly reduced by OM-89, with only 12 (19%) patients experiencing infections during the study compared with 32 (52%) for the pre-study period (p=0.002) (Table 6, Fig. 20).
- The need for antibiotics was significantly reduced, with 13% of patients (n=8) requiring antibiotic therapy during the study compared with 56% (n= 34) before the study (p=0.0002). Furthermore, the mean duration of antibiotic treatment was reduced from 3.2 to 2.0 days (p=0.0016) (Table 6, Fig. 20).
- **Only minor side effects, such as nausea and heartburn, were reported (3.2%), and all newborns were healthy with normal Apgar scores.**

Table 6: UTI recurrences and antibiotic treatment before and after treatment with OM-89.[71]

Number of patients before and after treatment with OM-89			
	Before study	**After study**	**p-value**
With UTI recurrence	32	12	0.002
Undergoing antibiotic therapy	34	8	0.0002

Adapted from Baertschi et al. (2003)

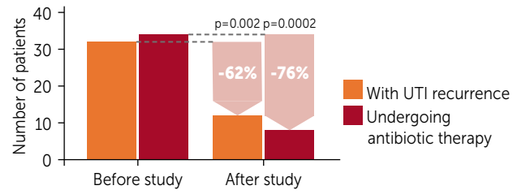


Fig. 20: Reduction in number of patients with UTI recurrence and undergoing antibiotic therapy after treatment with OM-89

Conclusions

OM-89 was well tolerated and reduced the number of recurrences, while minimizing the use of antibiotics in pregnant women. OM-89 is not contraindicated in pregnant women; however, OM-89 data are limited in these patients. As a precautionary measure, it is preferable to avoid its use during pregnancy.

Lettgen[72] 1996

Prevention of recurrent urinary tract infections in female children. OM-89 immunotherapy compared with nitrofurantoin prophylaxis in a randomized pilot study. Current Therapeutic Research

This randomized, open study was aimed at comparing the efficacy of long-term OM-89 therapy with that of nitrofurantoin in preventing UTIs in young girls.

Population
40 young girls, aged 6.5 years on average with ≥3 UTIs in the previous 12 months, were divided into two subgroups, with 22 randomly assigned to group A and 18 to group B.

Parameters and treatment modalities
- There were three consecutive 6-month treatment phases (Fig. 21).
- During phase I, all patients received nitrofurantoin (1 mg/kg/day); for phase II, group A was switched to 1 capsule of OM-89, while Group B remained on nitrofurantoin; for phase III, no treatment was given.

Results
During the 6 pre-trial months, two recurrences occurred on average in both subgroups. This figure fell to 0.05 during the first phase, while rising to 0.2 in the second phase in both subgroups. Mean values remained significantly ($p<0.0003$) lower than run-in, reaching 0.14 in the OM-89 and 0.24 in the nitrofurantoin subgroups (Table 7).

The enhanced immunologic defense obtained from OM-89 probably accounted for the long-term decrease in UTIs during phase III of the study.

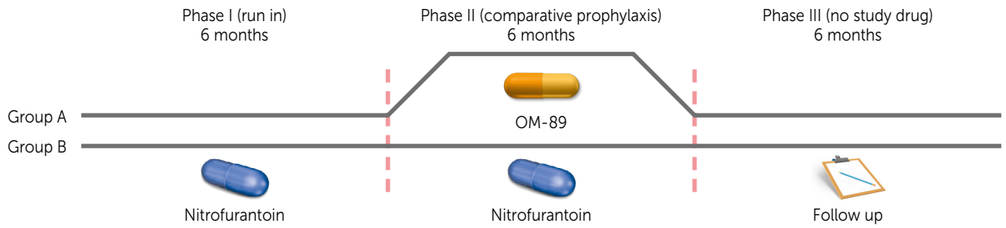


Fig. 21: Treatment regimens for patients in Groups A and B during the three phases of the 18-month trial [72]

From Lettgen 1996.

Table 7: UTIs experienced in patients treated with OM-89 compared to nitrofurantoin.[60]

Mean UTIs per patient (UTIs/patients)					
Group	**Baseline**	**Phase III follow-up (per protocol)**		**Phase III follow-up (best case)**	
		UTIs	p-value	UTIs	p-value
A (OM-89)	2.06 (35/17)	0.31 (4/13)	0.0015	0.24 (4/17)	0.0003
B (Nitrofurantoin)	2.00 (42/21)	0.15 (3/20)	0.0001	0.14 (3/21)	0.0001

Conclusions

OM-89 may be considered as an alternative to prophylaxis with nitrofurantoin in young girls, as its efficacy appears comparable to that of nitrofurantoin, but with a better safety profile and compliance, and without the risk of antibiotic resistance.

Czerwionka-Szaflarska et al.[51] 1996

Influence of OM-89 on sIgA level in urine in children with recurrent urinary tract infections. Archivum Immunologiae et Therapiae Experimentalis

This randomized, open-label study examined the influence of OM-89 on sIgA in the urine of children with recurrent UTIs.

Population
Overall, 38 children with UTI recurrences were randomly divided into two groups: Group I (n=25) treated with an antibiotic plus OM-89 and Group II (n=13) with an antibiotic alone.

Parameters and treatment modalities
- Analysis and culture of urine were performed at regular intervals.
- sIgA in urine was assessed in Group I at the start, during, and 3 months after stopping therapy, and in Group II at the start and 3 months after stopping therapy.

Results
- While bacteriuria incidence was similar in both groups during therapy (about 33%), 3 months after drug cessation, 16% of the OM-89 vs. 54% of the antibiotic control group had UTIs (Fig. 22).
- This favorable difference correlated with sIgA levels:
  - Before therapy, mean urinary sIgA levels were below normal (0.5 mg/l), being 0.20 mg/l in the OM-89 group and 0.26 mg/l in the control group.
  - 3 months after therapy, sIgA levels had not changed in the control (0.27 mg/l) group, but significantly rose to 0.33 mg/l ($p=0.02$) in the OM-89 group (Fig. 23).

Incidences of Bacteriuria

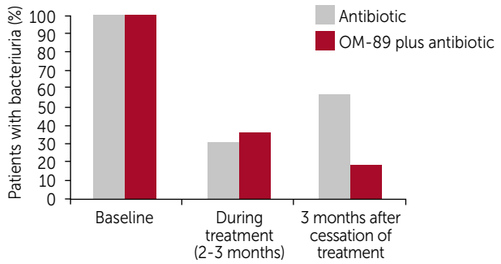


Fig. 22: Incidences of bacteriuria before, during, and 3 months after treatment with OM-89 plus antibiotic vs. antibiotic treatment alone [51]

Adapted from Czerwionka-Szaflarska et al. (1996)

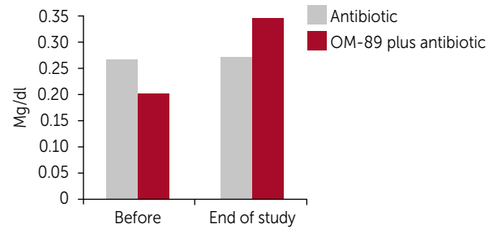


Fig. 23: sIgA in urine [51]

Conclusions

OM-89 in combination with an antibiotic is more effective than antibiotic therapy alone in children recurrent UTIs and was well tolerated. These results support the protective effect of OM-89 at the urothelium level, with the secretory IgA acting as an antigen-specific barrier to pathogens of the urinary tract.

SYSTEMATIC REVIEWS AND META-ANALYSES

The main purpose of meta-analyses is to increase the statistical power for primary endpoints and enhance the general applicability of findings. This may help resolve the uncertainties of smaller studies and draw attention to the strength and weaknesses of a research program.

Bauer et al.[66] 2002

Prevention of recurrent urinary tract infections with immunoactive E. coli fractions: a meta-analysis of five placebo-controlled double-blind studies. International Journal of Antimicrobial Agents

Five placebo-controlled, double-blind studies with similar study designs were included in this meta-analysis (Fig. 24) (n= 601).

Methodology

- The Wilcoxon-Mann-Whitney test was used, and p-values for a two-sided difference were calculated, as were Mann-Whitney statisticsi and their confidence intervals (CI).
- Criteria for retention included patients with recurrent UTIs and without anatomical abnormalities of the urinary tract.

Results

- OM-89 was statistically superior to placebo in reducing UTI frequency as well as dysuria, bacteriuria, and leukocyturia across studies, with the superiority being medically relevant (Mann-Whitney statistics). The value was 0.684, which shows an effect size between medium and large (Fig. 24).

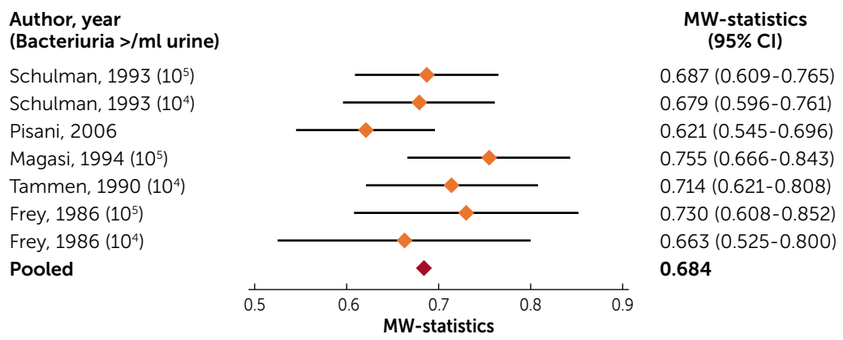


Fig. 24: Mann-Whitney (MW) statistics and confidence interval (CI) for UTI recurrence in OM-89 studies

From Bauer et al. 2002.

- **The safety and tolerability of OM-89 were defined as good by the investigators. Patients treated with OM-89 experienced minor adverse events (skin reactions and gastrointestinal discomforts) with the same frequency as patients in the placebo group. No serious adverse events were experienced by the patients treated with OM-89. The product was well tolerated, and patient compliance was excellent across the studies.**

Conclusions

This meta-analysis reinforces the conclusions of the clinical data presented above OM-89 as an effective and well-tolerated approach in the prevention of UTIs.

[i] The Mann-Whitney statistics are a measure of the superiority of the test group, with the following benchmarks for the relevance of superiority: 0.5 no difference, 0.56 small difference, 0.64 medium difference, and 0.71 large difference.

Naber et al.[67] 2009

Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis. International Journal of Immunotherapy

A second meta-analysis was conducted by another research group on a slightly different pool of five double-blind studies (N= 975).

Methodology

- The Mantel-Haenszel-Peto method was used for the analysis of ordinal data.
- Two-sided tests were applied, with $p \leq 0.05$ set as the threshold for significance.
- To be retained, a study had to be a randomised, placebo-controlled, clinical trial with the primary aim of reducing the number of UTIs over a period of 6–12 months.

Results

- UTIs were significantly lower after 6 months (mean value: -36%) and at the end of the studies (mean value: -39%) in OM-89 treated patients (Fig. 25), as was the use of antibacterials.
- Fewer OM-89-treated patients presented dysuria (RR=48%), leukocyturia (58%), and bacteriuria (RR[ii]=67%).
- There were significantly fewer OM-89-treated patients with UTIs at the end of the studies, regardless of study duration (42% of patients in the OM-89 group versus 62% in placebo group). Overall, the difference was -21% in favour of OM-89 (Fig. 26)
- **Regarding safety data, adverse events were slightly more frequent in OM-89-treated patients compared to placebo (+0.8%). No serious adverse effects related to OM-89 were reported.**

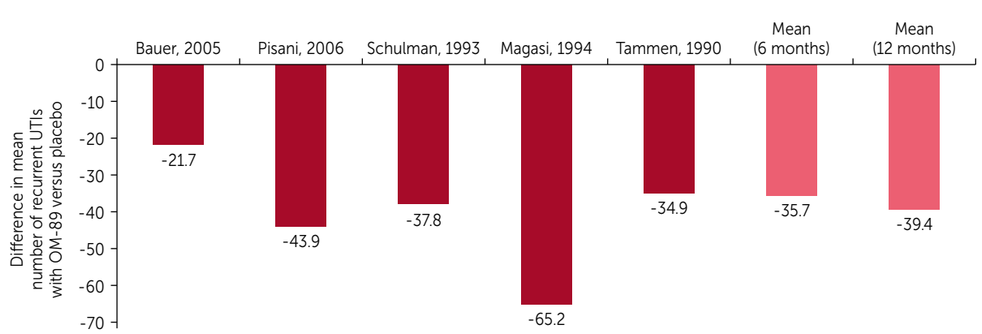


Fig. 25: Difference in mean number of recurrent UTIs with OM-89 versus placebo

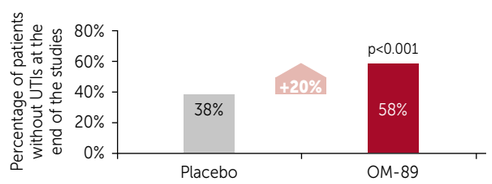


Fig. 26: Percentage of patients without UTIs: difference between OM-89 and placebo at the end of the studies [49]

From Naber et al. 2009.

Conclusions

Based on the results of this second meta-analysis, oral immunotherapy with OM-89 may be considered an effective and well-tolerated immunoactive prophylaxis under the conditions of daily practice.

[ii] RR = relative risk

Beerepoot et al.[73] 2013

Nonantibiotic Prophylaxis for Recurrent Urinary Tract Infections: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. The Journal of Urology

This 2013 meta-analysis reviewed 17 studies with 2'165 patients, and included 7 forms of non-antibiotic prophylaxis available for the management of recurrent UTIs. The OM-89 group comprised 4 studies with 891 patients.

Methodology

- Internal validity of included trials was assessed using the Jadad score.
- Random and fixed effects meta-analyses were performed on the risk ratios of at least 1 UTI with non-antibiotic prophylaxis compared to the control group using DerSimonian-Laird (DSL) and Mantel-Haenszel weights, respectively.
- Heterogeneity was assessed using the I-squared (I^2) statistic.

Results

- The risk ratio for the development of at least 1 UTI was significantly lower in the OM-89 group (RR 0.61), and mean number of UTIs was approximately half compared to placebo (Fig. 27).
- **The proportion of patients experiencing adverse events in the OM-89 group was comparable to that in the placebo group.**

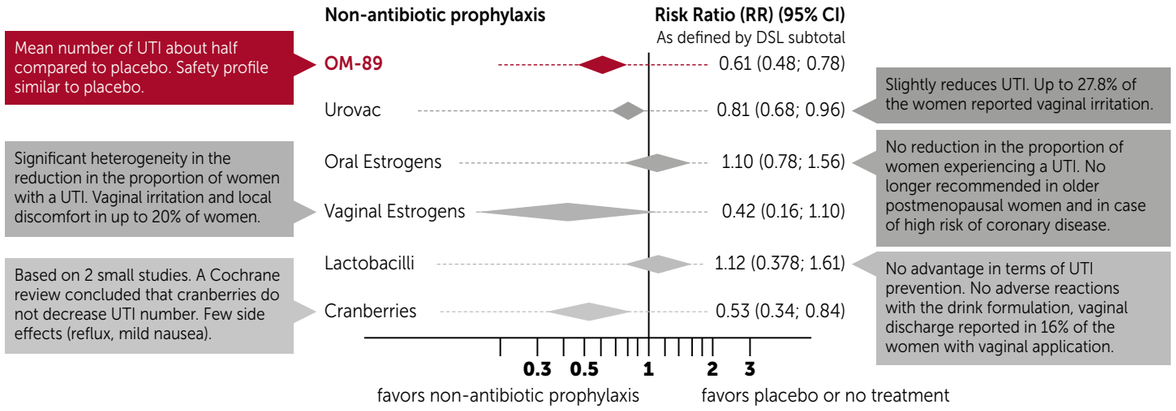


Fig. 27: Forest plot showing risk ratios and 95% confidence intervals (CI) (as defined by DSL random effects subtotal) for all forms of non-antibiotic prophylaxis included in the meta-analysis.[73] From Beerepoot et al. 2013.

Conclusions

Of all the different forms of non-antibiotic prophylaxis included in this systematic review, OM-89 was deemed the most promising to prevent recurrent UTIs. Furthermore, the investigators concluded that, whilst they were sometimes statistically significant, pooled findings for the other interventions should be considered tentative until corroborated by more research.

Neho et al.[74] 2016

Oral vaccine* (OM-89) in the recurrent urinary tract infection prophylaxis: A realistic systematic review with meta-analysis. Actas Urologicas Espanolas

This systematic review and meta-analysis reviewed 5 placebo-controlled, double-blind studies with 788 patients.

Methodology

- All meta-analyses were performed using Review Manager 5 with random effects model. Dichotomous data were compared using odds ratio (OR).
- Heterogeneity was assessed using the Chi-square test and was expressed by the I-squared (I^2) statistic.

Results

- Compared to the control group, results on the bacteriuria at 3 and 6 months were significantly in favor of OM-89 (p< 0.00001 and p= 0.0007 respectively)
- When comparing OM-89 and control groups, dysuria at 6 months occurred in 7.5% (29/385) and 18.9% of patients (73/385) respectively; OR were 0.35 in favor of OM-89. The difference between the two groups were statistically significant (P<0.00001)
- There was also significantly fewer episodes of acute cystitis after six months of OM-89 prophylaxis (p<0.00001).

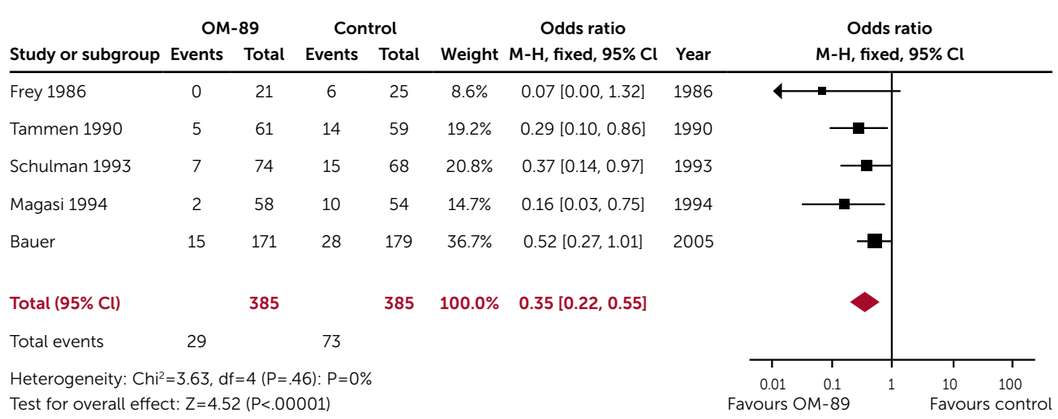


Fig. 28: Dysuria at 6 months.[74] From Neho et al. 2016.

Conclusions

- All results were in favor of OM-89, showing its efficacy in improving symptom severity and the rate of recurrent infections.
- The study authors concluded that further data are needed, including on patient quality of life and cost-effectiveness.

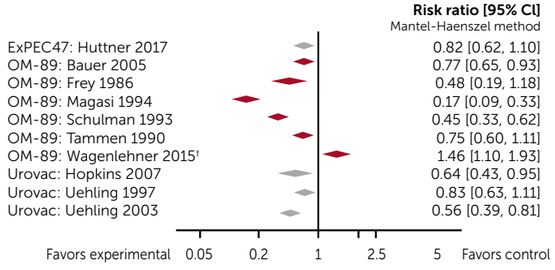
* OM-89 has a different mechanism of action from vaccines so is not considered one

Aziminia et al.[75] 2019
Vaccines* for the prevention of recurrent urinary tract infections: a systematic review. BJU International

This 2019 meta-analysis reviewed 10 studies with 1,780 patients and included 3 forms of non-antibiotic prophylaxis available for the management of recurrent UTIs. In total, 1,148 patients from 6 studies on OM-89 were included.

Methodology
- Internal and external study validity was assessed using the Grading of Recommendations Assessment, Development and evaluation (GRADE) method.
- Fixed effects meta-analyses were performed on the risk of UTI reoccurrence with non-antibiotic prophylaxis compared with the control group using the Mantel-Haenszel method, respectively.
- Heterogeneity was assessed using chi-squared testing and I-squared (I^2) percentage.

Results
- Results from individual studies examining the reoccurrence of UTIs with non-antibiotic prophylaxis compared with control favored OM-89 over other products (Fig. 28).
- The risk ratio for the reoccurrence of UTI was lower in the OM-89 compared with placebo group at 3 months (RR 0.67) and 6 months (RR: 0.78).
- The risk of dysuria at 6 months of follow-up was reduced with OM-89 compared with placebo (RR: 0.41).
- The incidence of adverse events was similar between OM-89 and placebo groups (RR: 1.00).



The difference in UTI reoccurrence rate was calculated for individual studies and pooled risk ratios (RR) were calculated using the Mantel-Haenszel method;
†Study used OM-89S, a different product which involved a modified production process.

Fig. 29: Forest plot showing risk ratios and 95% confidence intervals (CI) for UTI reoccurrence in studies reporting non-antibiotic prophylaxis included in the meta-analysis.[75] From Aziminia et al. 2019.

Conclusions

Analyses at 3 and 6 months suggested that OM-89 demonstrated the greatest reduction in UTI reoccurrence compared with placebo of the three non-antibiotic prophylactic products studied, with the greatest reductions at 3 months.

Key points

- OM-89 is an effective preventive treatment for recurrent UTIs, improving the clinical signs and symptoms.
- OM-89 reduces the risk of UTI recurrences and the need for antimicrobial agents.
- The beneficial effects of OM-89 can be prolonged with the use of the booster dosage regimen.
- OM-89 has a good safety-profile and well-tolerated across all the study populations, including pregnant and postmenopausal women, paraplegics and children regardless of type of pathogen.
- OM-89 is well tolerated when administered in concomittance with antibiotics during an acute symptomatic infection.

* OM-89 has a different mechanism of action from vaccines so is not considered one

Impact on patient quality of life

Renard et al.[76] 2014
Recurrent lower urinary tract infections have a detrimental effect on patient quality of life. International Journal of Gynecology & Obstetrics

This international (Egypt, Germany, Lebanon, Peru, Poland, Portugal, and Switzerland), prospective, 6-month, observational, multi-center, epidemiological pilot study was conducted in order to explore quality-of-life indicators and assess their relationship to UTI recurrences under preventive treatment.

Population
- 575 patients were enrolled, with a mean of 2.7 UTIs during the previous 6 months.
- About 62% and 74% of patients presented anxiety or depressive symptoms (Hospital Anxiety and Depression score [HAD]) as well as social or functional limitations [Leicester score], respectively.

Results
- During the survey, 95% of patients were prescribed preventive treatment for their UTI, with 94% receiving OM-89.
- During the survey, there was a significant reduction in UTIs from baseline (59%; p≤0.0001)
- Parallel to the reduction in UTIs, there were significant improvements in anxiety (36%), depression (25%),[iii] and global HAD (32%), as well as feeling (55%), activity (33%), and global Leicester (44%) scores (p≤0.0001). Improvements in HAD and Leicester scores as well as reduction in UTIs (Fig. 29).
- UTI reduction correlated with improvements in anxiety and depression scores. There was a correlation trend between the reduction in the numbers of UTIs at the end of the study compared to the 6 months prior to study entry and a reduction in the anxiety, depression, total HAD scores, and total Leicester scores registered from Day 0 to Day 180. This suggests a lessening of emotional problems, social and functional handicaps with decreasing UTI incidence.

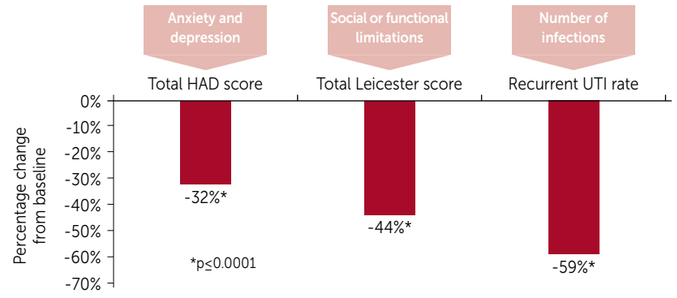


Fig. 30: Improvement in quality of life (as reflected in HAD scores and total Leicester scores) alongside a reduction in number of UTIs between baseline versus the end of the study (Day 180).[76]

Adapted from Renard et al. 2014.

Conclusions

- Suffering from recurrent UTIs has a negative impact on patient quality of life.
- Appropriate preventive treatment (including with OM-89) leads to a significant reduction in UTIs.
- Reduction in UTIs was shown to be associated with an improvement in quality of life indicators.

Key points

- Immunoprophylaxis with OM-89 improves quality of life as measured by anxiety and depression scales, as well as the impact on social or functional activities.

[iii] An anxiety score (AS) <8 is considered as normal, AS 8-10 as mild anxiety, AS 11-15 as moderate anxiety, and AS 16-21 as severe anxiety; a depression score (DS) <8 is considered as normal, DS 8-10 as mild depression, DS 11-15 as moderate depression, and DS 16-21 as severe depression.

Safety profile

OM-89 was first registered in Switzerland in 1987 and at present, it is marketed in more than 55 countries. It is estimated that around ~5.8 million patients have been treated with OM-89.[77]

Animal toxicity studies
OM-89 has shown to be remarkably well-tolerated in the extended program of animal safety studies. Tests performed *in vivo* reported no effects on mutagenicity and teratogenicity.

Clinical studies
- In clinical trials (N=474), OM-89 has shown a favorable safety profile with an overall incidence of adverse events similar to those observed with placebo.[55–60]
- OM-89 has shown to be well-tolerated in both adults and children aged over 4 years, with an overall adverse event incidence of 4% reported in clinical trials regardless of the causality.[33]
- The majority of events were gastrointestinal disorders, such as nausea, diarrhea, and dyspepsia, most likely caused by propylgallate or glutamate.
- Patient compliance was excellent throughout the studies.

Meta-analyses
OM-89 has been found to have a similar safety and tolerability profile to placebo.[73,75]

Pharmacovigilance
- This favorable tolerability profile was confirmed by close post-marketing pharmacovigilance monitoring.
- Since its launch in 1987, ~5.8 million patients have been treated with OM-89. In total, 2104 adverse events have been reported in 931 patients, equating to an adverse event rate of 161 cases per 1 million patients treated. Based on estimated patient exposure, the observed frequency of adverse events related to OM-89 is very low.

Key safety points
- The overall incidence of adverse events (regardless of causality) in clinical trials is approximately 4%
- Most indesirable effects were gastrointestinal disorders
- Since its launch in 1987, ~5.8 million patients have been treated with OM-89

Conclusions

OM-89 presents a favorable risk-benefit profile, which has remained unchanged over the last two decades.

Overall Key Points
- OM-89 is an effective preventive treatment for recurrent lower UTIs and has shown to reduce the need for antibiotics.
- OM-89 is recommended by the EAU guidelines (Recommendation «Strong», level of evidence 1a) and other several regional and local guidelines and consensus papers.
- OM-89 displays a favorable safety profile.
- OM-89 has a convenient dose regimen/posology is 1 capsule daily for 3 months.
- OM-89 shows a good efficacy and safety profile across several specific populations (i.e. children, pregnant and postmenopausal women, spinal cord injury patients).

Conclusions

OM-89 is well documented and well tolerated; the present studies and meta-analyses provide convincing evidence that immunoprophylaxis with OM-89 can be used as a first line strategy for UTI prophylaxis and antibiotic sparing in at-risk patients, as recommended in the EAU Guidelines on Urological Infections.



"Thank you for your help!"

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77 Data on file

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