Immunoactive prophylaxis of recurrent urinary tract infections: a meta-analysis

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CRD summary

The review concluded that the oral bacterial lysate immunostimulant, OM-89, was safe and efficacious for preventing recurrent urinary tract infections, but that more research is required. Overall, the authors' cautious conclusions seem appropriate, but their reliability is uncertain given the potential for bias in the review methods.

Authors' objectives

To assess the efficacy and safety of immunostimulants based on bacterial lysates in the prophylaxis of recurrent urinary tract infections.

Searching

The following databases were searched up to September 2008: TOXLINE, MEDLINE, HealthSTAR, AIDSLINE, CANCERLIT, EMBASE, AMED, the Cochrane Library, DART (Developmental and Reproductive Toxicology), HSDB (Hazardous Substances Data Bank), IRIS (Integrated Risk Information System), ITER (International Toxicity Estimates for Risk), GENE-TOX, ChemIDplus and Haz-Map. Search terms were reported. Bibliographies of articles and reviews were also searched and experts and manufacturers contacted.

Study selection

Eligible studies were randomised, placebo-controlled clinical trials (RCTs) of bacterial lysate immunostimulants with the primary aim of reducing the number of recurrent urinary tract infections over a period of six to 12 months. Participants were included if they were suffering from an acute recurrent urinary tract infection and had a history of recurrent urinary tract infections. Exclusion criteria included medical conditions predisposing to recurrent urinary tract infections.

Outcomes included the number of recurrent urinary tract infections during the trial, the proportion of patients without recurrent urinary tract infections, consumption of antibacterials, the presence of dysuria at final visit, leukocyturia, bacteriuria and safety.

The primary intervention was OM-89 (Uro-Vaxom), an oral formulation of a bacterial lysate immunostimulant, given once daily for three months, with follow-up of an additional three months. The comparators were placebo formulations. A secondary intervention was a vaginal formulation. The definition of a recurrent urinary tract infection was variable and, in one trial, was not defined. The included trials were preliminary studies with small numbers of participants. Participants included both men and women, although men comprised only 7% of the total population; ages ranged from 16 to 82 years.

One reviewer independently assessed the studies for inclusion in the review. Disagreements were resolved by discussion with other review authors.

Assessment of study quality

The authors stated that no formal validation process was employed. They did note whether trials were carried out under good clinical practice, whether an intention-to-treat (ITT) analysis had been performed, and if analysis had been per protocol.

Data extraction

Data were extracted from each trial on the number of recurrent urinary tract infections, proportion of patients without recurrent urinary tract infections, consumption of antibacterials for recurrent urinary tract infections, and incidence of adverse events. Data were extracted employing a cut-off of six months, as well as after six months and twelve months and used to calculate the odds ratio (ORs), and corresponding 95% confidence intervals (CIs), for the proportion of patients without recurrent urinary tract infections, and incidence of dysuria, leukocyturia and bacteriuria; and the standardised mean difference (SMD) and 95% confidence interval (consumption of antibacterials for recurrent urinary

tract infections).

The authors did not state how many reviewers performed the data extraction.

Methods of synthesis

For the mean number of recurrent urinary tract infections, the pooled weighted mean difference (WMD) and corresponding 95% confidence intervals were calculated using both fixed-effect and random-effects meta-analysis. For the proportion of patients without recurrent urinary tract infections, the authors calculated the pooled odds ratio and corresponding 95% confidence intervals using an unspecified meta-analysis. For the consumption of antibacterials for recurrent urinary tract infections, the pooled standardised mean difference and corresponding 95% confidence intervals were calculated using a random-effects meta-analysis. For incidence of dysuria, leukocyturia and bacteriuria at final visit, the pooled odds ratio and corresponding 95% confidence intervals were calculated using an unspecified meta-analysis.

Unspecified tests for heterogeneity and over-all effect were employed.

Results of the review

Five RCTs were included in the review (n=895). Three trials were reported as performed under good clinical practice. Two trials used intention-to-treat analysis, and all trials were analysed per protocol (excluding protocol violators).

Mean number of urinary tract infections: The bacterial lysate immunostimulant OM-89 significantly reduced the number of urinary tract infections compared with placebo at six months (WMD -0.26, 95% CI -0.36 to -0.16; fixed-effect model). Significant heterogeneity was detected between the trials (p=0.0004).

Proportion of patients without recurrent urinary tract infections: A significantly greater number of patients treated with OM-89 had no recurrent urinary tract infections over six months (OR 0.46, 95% CI 0.36 to 0.59). Significant heterogeneity was detected between the trials (p=0.001).

Consumption of antibacterials for urinary tract infections: OM-89 was associated with a significant reduction in the use of antibacterials (SMD -0.29, 95% CI -0.44 to -0.14; n=863). There was no evidence of statistical heterogeneity.

Findings as the end of the trials: The incidence of dysuria (OR 0.43, 95% CI 0.28 to 0.66; n=758) and leukocyturia (OR 0.45, 95% CI 0.28 to 0.72; n=389) at final visit were significantly lower in the patients taking OM-89. The incidence of bacteriuria was lower with OM-89 but findings were inconsistent between trials.

Safety: No serious adverse events were attributed to OM-89. Adverse events were slightly more frequent with OM-89 (+0.8%) than with placebo and led to a slight increase in withdrawal from the trials (+0.6%). In general, adverse events were uncommon and did not differ significantly between placebo and OM-89.

Authors' conclusions

The bacterial lysate immunostimulant OM-89 reduced the number of recurrences of urinary tract infections and subsequent antibacterial treatment when compared with placebo, but further studies are required to develop optimal treatments.

CRD commentary

The review addressed clear research questions and inclusion criteria appear to be appropriate. Relevant sources were searched and attempts were made to locate unpublished material. It was unclear if studies were restricted by language, so language bias cannot be ruled out. Publication bias was not assessed. Methods were used to minimise reviewer error or bias in the selection of trials, but it was unclear what methods were used to reduce data extraction errors. Validity was not assessed systematically, so it was difficult to judge the potential risk of sources of bias in the selected trials. A minor data discrepancy was noted in the tables. Methods of analysis appeared appropriate but were not always specified. Significant heterogeneity between trials means that the results should be interpreted with caution.

Overall, the authors' cautious conclusions seem appropriate, but their reliability is uncertain given the potential for bias in the review methods.

Implications of the review for practice and research

Practice: The authors did not state any implications for practice.

Research: The authors stated that further research is required to determine if gender, type of infection, secretor status, hormonal status, concentration of Tamm-Horsfall protein or other variables are predictors of response to OM-89. Further studies directly comparing antimicrobial prophylaxis with immunoactive prophylaxis are also needed. The authors noted that such studies are planned.

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