Treatment of recurrent urinary tract infections (UTIs) is an urgent problem. Three most important causes of recurrences in females: anatomical and functional disorders, sexually transmitted infections and postmenopause associated with a number of changes that cause a decrease in resistance to intestinal pathogens [1].

Current guidelines offer a variety of approaches to reduce UTI recurrences, including the use of natural herbal components. However, their use has no certain evidence base. For example, cranberries are considered effective when containing minimum 36 mg of proanthocyanidin (PAC) A (level of evidence: 1b, grade of recommendation: C) [2]; a lower dose is not effective. This was one of the reasons for the exclusion of cranberry products from the guidelines of the European Association of Urology (EAU) in 2014 [3].

However, combined cranberry-containing products are still popular due to their safety and quite convincing efficacy. Our attention was drawn to a study conducted by P. Koradia et al. in premenopausal women with recurrent UTIs, which results were presented in 2019 [4]. This study demonstrated the effectiveness of Bio-Kult Pro-Cyan in the prevention of recurrent UTIs in premenopausal women. These data require further well-designed trials to clarify possible benefits.

Keywords: Lactobacilli; urinary tract infection; postmenopausal period
Purpose of the study: to investigate the efficacy of Lactiale Uro in the prevention of recurrent UTIs in postmenopausal women.

Materials and methods

An open-label, prospective, randomized, multicenter, comparative study, LACMUS, was conducted in 61 patients (mean age 56.1 ± 1.5 years): 31 women were in the Lactiale Uro group and 30 in the control group not receiving Lactiale Uro.

The study design was completely reproduced from the original study by P. Koradia et al. [4], which became a prototype, with the only amendment — all patients were documented postmenopausal. The mean time after the last menstruation was 3.2 ± 1.5 years. In addition, the studied product Lactiale Uro had a different composition, compared to BKPro-Cyan, and contained vitamin A.

The primary endpoint was the proportion of subjects with recurrent UTI episodes at the end of the study.

Exclusion criteria: active UTI; use of any antibiotic for 2 weeks after screening; known allergy to any ingredient in the study product; use of any natural product within a month prior to the study; positive pregnancy test; presence of the menstrual cycle; concomitant use of corticosteroids, anticoagulants, antidepressants, other mood-stabilizing drugs, or any medications that may interact with the supplement; significant comorbidities or conditions, including psychiatric, cardiac (including poorly controlled hypertension), renal (including anatomical disorders, catheterization, kidney stones, or kidney transplantation); hepatic (including hepatitits B or C), neurological, endocrine, metabolic (including diabetes), or lymphatic diseases, which, according to the physician, may adversely affect the subject’s participation in the study; immunodeficiency disorders (including human immunodeficiency virus); and active participation in any clinical trial within one month after the beginning of the study.

Drug administration: immediately after recovery from UTI, the next day after the last dose of an uroantiseptic (antibiotic), Lactiale Uro, 1 capsule twice daily with meals, was prescribed as a prophylactic treatment according to the instructions for use. Prescription was based on the manufacturer’s instructions, which specified the period of administration as 14–21 days or as prescribed by a doctor.

The duration of the study was 6 months, 26 weeks of active follow-up of the patients. For the first month of treatment, JSC Farmak provided free Lactiale Uro as an encouraging step. The patients did not receive any fees for the inclusion or participation in the LACMUS study.

The efficacy of Lactiale Uro was assessed based on the number of patients from the group who did not develop recurrent UTIs, which was determined according to the criteria of the EAU, 2019 [5]. Lactiale Uro was not discontinued in cases of UTI exacerbation.

Each patient gave an informed consent for treatment. The local ethics committee did not evaluate the study because it did not use a pharmacological agent, as Lactiale Uro is a dietary supplement. However, each doctor who prescribed the product confirmed the possibility of its long-term use, provided a monitoring of women according to the study protocol.

At the end of the study, each patient answered 3 questions about quality of life, including:
- comfort regarding urogenital system;
- general impression on the efficacy of UTI treatment.

The evaluation was performed using a 10-point score.

Statistical processing was carried out using Chi-Square Test Calculator [6]. However, for a better comparison with the prototype, we used the same approach, i.e. descriptive statistics was used to compare findings in the two treatment groups, and these included counts and percentages for categorical data. Continuous data were summarized using mean, standard deviation (SD), median, and range (minimum and maximum values) [4].

Results and discussion

At the end of the study, 31 subjects and 30 patients from the control group were included in the analysis (Table 1).

According to Table 1, 84.4 % of the selected patients were included in the study, 91.8 % completed the study.
Four patients discontinued the study for organizational reasons.

Statistical analysis comparing the efficacy of treatment is shown in Table 2.

According to Table 2, the use of Lactiale Uro resulted in a significant reduction in the number of both UTI episodes and women who experienced them. The number of recurrent episodes decreased almost fourfold (3.66). This effect was quite expected, as the amount of cranberry active substance complied with the evidence-based recommendations of the European Association of Urology (2013). Further cancellation of the recommendations regarding cranberries, in our opinion, is based on incorrect prescriptions and disregarded risk factors for the process exacerbation.

Apart from cranberries, there are many approaches in the reduction of UTI recurrences, in particular, development of autovaccines [7] or officinal preparations [8]. These measures are aimed at pathogen eradication through the body immune defense. However, adding active ingredients to cranberries can help the immune system to form local reactions. This is exactly what we observed in the analysis of recurrence characteristics in the LACMUS study.

Table 3 shows the number of UTI episodes, time to their occurrence, duration and the need for antimicrobial therapy. The presented data have significant differences, which indicate the efficacy of the used approach to Lactiale Uro administration. A very important parameter was the presence of bacteriuria at the end of the study, it was observed in 2 patients from the study group and 7 patients from the control group ($X^2 (2, n = 61) = 2.074, p = 0.16776$).

However, our data showed the results not as impressive as those of the selected prototype [4]. When we started the study, we expected a higher percentage of women to be able to maintain a recurrence-free course. Possible explanations may be the excessive number of risk factors in postmenopausal patients compared to premenopausal ones and possible non-compliance of the individuals with the treatment schedule for Lactiale Uro during 5 months of self-administration of the product at their own expense.

At the same time, the use of Lactiale Uro as a biological supplement showed very promising results: an almost

| Number of subjects | Lactiale Uro | No product | Total |
|--------------------|-------------|------------|-------|
| Screened, n        |             |            | 77    |
| Screen failure, n  |             |            | 12    |
| Randomized, n      | 32          | 33         | 65    |
| Completed the study, n (%) | 31 (96.8) | 30 (90.9) | 61 (93.8) |

Population analysis, n (%)

|          | Lactiale Uro | No product | Total |
|----------|-------------|------------|-------|
| FAS      | 31 (97.8)   | 30 (100.0) | 61 (100) |
| PP       | 28 (90.3)   | 28 (93.3)  | 56 (91.8) |

Notes: n — number of subjects in the given category; FAS — full analysis set; PP — per-protocol.

| Population/visit | Lactiale Uro | No product | Lactiale Uro vs No product (P-value) |
|------------------|--------------|------------|-------------------------------------|
| FAS population, number of subjects | 31           | 30         | Comparing number of patients $X^2 (2, n = 61) = 2.074, p = 0.149793$ |
| Visit 6 (week 26): n (%) [number of recurrent UTI episodes] | 3 (9.7) [4] | 7 (23.3) [11] | Comparing number of patients $X^2 (2, n = 61) = 4.642, p = 0.31184$ |
| Chi-square test, 95% CI | 5.08 [0.85] | 4.92 [0.88] |                       |
| PP population, number of subjects | 28           | 28         | Comparing number of patients $X^2 (2, n = 56) = 1.948, p = 0.162821$ |
| Visit 6 (week 26): n (%) [number of recurrent UTI episodes] | 3 (10.7) [4] | 7 (25.0) [11] | Comparing number of patients $X^2 (2, n = 56) = 4.4612, p = 0.34661$ |
| Chi-square test, 95% CI | 5.00 [0.80] | 5.00 [0.80] |                       |
twofold reduction in the number of women with recurrent UTIs during supplement administration was impressive. Discontinuations of treatment due to side effects of the product and quality of life assessments regarding urogenital complaints were also important. The mean score of satisfaction regarding the urogenital system was 7 out of 10 in those taking Lactiale Uro and 4 out of 10 in those who were not prescribed this therapy. Presumably, a long-term use of Lactobacilli, contained in the product, and vitamin A helped maintain a healthy microflora of the vagina.

Administration of herbal products can significantly improve the course of UTI, sometimes competing with antibiotic therapy [9]. Such studies have recently become more active, which is associated with an increase in antibiotic resistance [10]. However, it should be noted that at least 3 factors contribute to recurrences in postmenopausal women: estrogen depression, changes in the anatomy of the urinary tract, and decreased sexual activity [11, 12].

The LACMUS study, in our opinion, has become a litmus test that demonstrates the capabilities of a dietary product in achieving medical goals. Excellent tolerability of Lactiale Uro, an almost 4-fold reduction in the number of UTI episodes and improvement of the quality of life in postmenopausal women demonstrate the right choice in the search for optimal health status in women over 49 years. However, further research may provide additional data on the efficacy and feasibility of a long-term use of the product.

Table 3. Secondary efficacy endpoints at the end of 26 weeks of treatment

| Parameter | Lactiale Uro | P-value | No product |
|-----------|-------------|---------|------------|
| **Summary of UTI episodes at the end of 26 weeks of treatment** | | |
| FAS population | N = 32 | | N = 33 |
| Number of episodes | | |
| Visit 6 (week 26), n (%) | 0 | 31 (96.6) | 30 (90.9) |
| 1 | 2 (6.45) | 5 (16.6) |
| 2 | 2 (6.45) | 6 (20.0) |
| PP population | 28 | 28 |
| Visit 6 (week 26), n (%) | 0 | 27 (96.4) | 28 (100) |
| 1 | 2 (7.4) | 5 (17.9) |
| 2 | 2 (7.4) | 6 (21.4) |
| P-value FAS population (Fisher’s exact test) for 0 and 1 UTI [95% CI] | | 0.152 |
| P-value FAS population (Fisher’s exact test) for 0 and 2 UTI [95% CI] | | 0.093 |
| **Time (days) to first episode of UTI from randomization** | | |
| FAS Population, N | 31 | 30 |
| n | 4 | 11 |
| Mean (SD) | 136 | 27 |
| Median | 24.3 | 18.4 |
| P-value (Student’s t-test) [95% CI] | | P = 0.003810 (t = 3.58) |
| **Duration (days) of active UTI episode** | | |
| FAS Population, N | 31 | 30 |
| n | 4 | 11 |
| Mean (SD) | 5 | 11 |
| Median | 1 | 2 |
| Min, Max | 4, 6 | 4, 30 |
| P-value (Student’s t-test) [95% CI] | | P = 0.019916 (t = 2.66) |
| **Duration (days) of antibiotic treatment for an active UTI episode** | | |
| PP Population, N | 28 | 28 |
| Number of subjects with an active UTI episode and requiring antibiotic course | 4 | 10 |
| P-value (Fisher’s exact test) [95% CI] | | 0.046289 |

Notes: N — number of subjects in given analysis population; n — number of subjects with UTI episode.
A product similar to Lactiale Uro, Pro- Cyan (BKPro- Cyan), containing probiotic strains (Lactobacillus acidophilus PXN 35, Lactobacillus plantarum PXN 47) and cranberry extract (36 mg/d PACs), is available on the world market for the prevention of recurrent uncomplicated UTIs in premenopausal women. However, various products with similar compositions, based on the presented and prototype studies, are expected to be effective in pre- and menopausal women.

Limitations of the study: small number of patients, lack of placebo control.

Conclusions

1. Lactiale Uro in the LACMUS study showed a significant reduction in the number of recurrent UTI episodes in postmenopausal women compared to those who did not receive it. Lactiale Uro was very well tolerated during a 6-month course; there were no discontinuations of the product.
2. Lactiale Uro showed a significant reduction in urogenital complaints in women with recurrent UTIs, which is probably due to the comprehensive action of the product.
3. The above findings allow us to consider Lactiale Uro as an effective agent for the prevention of recurrent UTIs in postmenopausal women, administered as 1 capsule twice daily for at least 6 months.

Conflicts of interest. Authors declare the absence of any conflicts of interests and their own financial interest that might be construed to influence the results or interpretation of their manuscript. JSC Farmak sponsored the first month of Lactiale Uro administration, as well as summary and presentation of the materials of the investigator-initiated study.

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Information about authors

Dmytro D. Ivanov, MD, PhD, Professor, Head of the Department of Nephrology and Renal Replacement Therapy, Shupyk National Medical Academy of Postgraduate Education, Kyiv, Ukraine; https://orcid.org/0000-0003-2609-0051

Olexiy M. Korzh, MD, PhD, Head of the Department of General Practice — Family Medicine, Kharkiv Medical Academy of Postgraduate Education, Kharkiv, Ukraine

Ivanov D.D.1, Korzh O.M.2
1Національна медична академія післядипломної освіти ім. П.Л. Шупика, м. Київ, Україна
2Харківська медична академія післядипломної освіти, м. Харків, Україна

Лактіалє Уро в профілактиці сечової інфекції в постменопаузі: результати дослідження LACMUS

Резюме. Мета: оцінити ефективність і безпеку Лактіалє Уро, препарату, що містить два штами Lactobacilli, екстракт журавлині та вітамін А, в запобіганні повторним інфекціям сечових шляхів (ICШ) у жінок у постменопаузі (дослідження LACMUS). Матеріали та методи. Це було рандомізоване про- спективне багатоцентрове дослідження. Суб'єкти отримували Лактіалє Уро двічі на день протягом 26 тижнів після одужання від ICШ; контрольна група препарат не отримувала. Первісною кінцевою точкою була частка пацієнтів із повторними епізодами ICШ у кінці дослідження. Результати. Сім'яти сім жінок проішли обстеження. у дослідженні вийшли 65, а за- вершила його 61 пацієнка. Через 26 тижнів у значно меншій кількості жінок відзначені повторні ICШ в різних групах (14,6% проти 20,2% в групі-контроль; p = 0,01). Загальна кількість повторних ICШ у групі-контроль була в більшій мірі (74,7% проти 46,7% в групі-різ). Висновки. Лактіалє Уро порівняно з плацебо був позитивним для усіх параметрів, зокрема для епізодів ICШ. У групі, що отримувала Лактіалє Уро, відзначено більшу кількість повторних ICШ, що свідчить про її ефективність у захисті від ICШ у жінок у постменопаузі. У перспективі інноваційних протитуберкульозних лікарських засобів.

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Лактиале Уро в профілактиці мочевої інфекції в постменопаузі: результати навчання LACMUS

Резюме. Цель: оцінити ефективність і безпеку Лактиале Уро, препарата, що містить два штами Lactobacilli, екстракт клюкви і вітамін А, в профілактиці повторних інфекцій мочових трактів (ІМП) у жінок в постменопаузі (навчання LACMUS).

Матеріали і методи. Це було рандомізоване проективне мультицентрове навчання. Суб'єкти отримували Лактиале Уро двічі на день протягом 26 тижнів після досягнення рівень ІМП; контрольна група не отримувала лекарства. Першою кінцевою точкою була частина більшості жінок, які вишіли ІМП.

Результати. Семицівствість жінок коли проходило навчання, в навчанні взяли участь 65 жінок, а завершила його 61 жінка. Після 26 тижнів більш низько рівень повторних ІМП в порівнянні зі тими, хто не отримувала лікування (9,7 проти 23,3 %; P < 0,05). Використання Лактиале Уро обумовлювало статистично значиме підвищення, такі як нижні тривалості епізодів ІМП (12,9 проти 36,6 %; P < 0,05), більше часу до першого епізоду ІМП (136 проти 27 днів; P = 0,0038), меншу тривалість активного епізоду ІМП (5 проти 11 днів; P = 0,0199) і меншу тривалість антибактеріальної терапії активного епізоду ІМП (4 проти 10 днів; P = 0,0462).

Висновки. Лактиале Уро був безпечним та ефективним у профілактиці повторних ІМП у жінок у постменопаузі. Ці дані вимагають подальших добрих розроблених досліджень для з'ясування можливих переваг.

Ключові слова: Lactobacilli; інфекція сечових шляхів; постменопаузальний період.