ORIGINAL RESEARCH

DOI: 10.5336/jcog.2021-85924

The Efficacy and Safety of Gynomax® XL Vaginal Ovule in the Treatment of Common Vaginal Infections: A Single-Arm Clinical Trial, Gyno-Türk

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The summmary of this study was presented with an oral presentation in "COVID-19 Pandemisi Sürecinde Kadın Sağlığı ve Üreme Sağlığına Bakış Sempozyumu" in 26-27 December 2020, Online.

ABSTRACT Objective: The objective of this study was to evaluate the efficacy, safety, and tolerability of Gynomax® XL vaginal ovule in the treatment of bacterial vaginosis (BV), candidal vulvovaginitis (CVV), trichomonal vaginitis (TV), and mixed vaginal infections (MVI). **Material and Methods:** A total of 98 women diagnosed clinically with BV, CVV, TV, or MVI have completed this study. Patients were given Gynomax® XL for 3 consecutive days, and approximately 10 (+/-5) days after the treatment, a follow-up visit was conducted. In addition to the clinical examinations, vaginal swab samples were collected in both visits for microbiological tests. **Results:** Based on the clinical diagnosis of the investigators, most of the patients had MVIs (54.1%), followed by BV (24.5%) and CVV (20.4%) at the baseline visit. One (1.0%) patient was diagnosed as having TV. According to the microbiologic examination results, 44 (44.9%) patients had BV, 20 (20.4%) had CVV, and 13 (13.3%) had MVIs. According to the clinical findings, overall complete recovery (CR) was observed in 76.5% of the patients and according to the microbiologic findings, overall CR was observed in 85.7% of the patients. Microbiologic results evaluated by each diagnostic criterion showed that CR was detected in 93.2%, 85.0%, and 61.5% of the patients with BV, CVV, and MVIs, respectively. There were no serious or non-serious adverse events leading to patient withdrawal or treatment discontinuation during this study. **Conclusion:** Gynomax® XL vaginal ovules administered once daily for three consecutive days provide effective and safe treatment in patients with BV, CVV, and MVIs.

Keywords: Efficacy; Gynomax; lidocaine; safety; tinidazole; tioconazole

Vulvar and vaginal infections are among the most common medical problems in the general practice of gynecologic diseases. There are 3 common types of vaginitis: bacterial vaginosis (BV), candidal vulvovaginitis (CVV), and trichomonal vaginitis (TV).[1] Vaginitis due to simultaneous infection with at least 2 pathogens [mixed vaginal infection (MVI)] is quite common and accounts for approximately 30% of all cases.[2-5]

In general practice, the diagnosis of the underlying cause of vaginitis is usually made based on clinical features, and most of the time the treatment is started without microbiologic verification of the infectious agent. In such cases where the cause of vaginitis may be of mixed origin and microbiologic investigation is not available for the detection of all concomitant infections, a fixed-dose combination treatment may provide an efficient and successful treatment for BV, CVV and TV.

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Peer review under responsibility of Journal of Clinical Obstetrics & Gynecology.

Received: 27 Aug 2021 ***Accepted:*** 04 Jan 2022 ***Available online:*** 18 Jan 2022

Based on these facts, a new vaginal ovule (Gynomax® XL, Exeltis İlaç, İstanbul, Turkey) which contains tinidazole (300 mg), tioconazole nitrate (200 mg) and lidocaine (100 mg) was developed to be administered once daily for 3 consecutive days for the treatment of common vaginitis.

Tinidazole is an antibiotic agent used in treatment of majority of the vaginal infections.[6-9] Tioconazole is a synthetic antifungal agent used to treat vaginal yeast infections and it reduces vaginal burning, itching, and discharge.[10-14] Lidocaine is a well-established, effective, and safe local anesthetic agent, which is well absorbed by the tissues, therefore provides a rapid anesthetic activity.[15]

Due to the presence of two bioactive components in the form of an ovule for intravaginal administration, the rate of adverse events (AEs) of Gynomax® XL vaginal ovules is expected to be infrequent when compared with systemic treatments.

The aim of this study was to evaluate the efficacy and safety of Gynomax® XL vaginal ovule in the treatment of BV, CVV, TV and MVIs.

MATERIAL AND METHODS

This study was designed as a multi-center, open-label, single-arm, prospective, phase IV study and conducted in 5 gynecology and obstetrics clinics (Ege University Faculty of Medicine, İzmir; İzmir University of Health Sciences Tepecik Training and Research Hospital, İzmir; Hisar Hospital, İstanbul; University of Health Sciences Dr. Zekai Tahir Burak Training and Research Hospital, Ankara; University of Health Sciences Etlik Zübeyde Hanım Training and Research Hospital, Ankara) located in 3 major cities in Turkey. The study was registered in a publicly accessible database (ClinicalTrials.gov identifier: NCT03839875) before patient recruitment and after obtaining the approval of the Ege University Faculty of Medicine Clinical Research Ethics Committee (approval date and number: 10 January 2019, No: 19-1/9). All procedures performed in this study were in accordance with the principles of Helsinki Declaration and its later amendments. All patients were informed about the procedures of the study and a written informed consent was obtained before performing study-related procedures.

Pre-menopausal, symptomatic female patients with vaginal discharge aged 18-45 years who were clinically diagnosed as having BV, CVV, TV or MVI were consecutively enrolled in the study. Pregnant or lactating patients, women who are virgins, or patients with vaginismus, endometriosis, deep dyspareunia, urinary tract infection, undiagnosed vaginal bleeding, bleeding disorders, and genital tumors were excluded.

At the baseline visit, a detailed clinical and gynecologic examination and vaginal pH measurements were performed in the study centers. Symptoms and signs as mentioned in The International Union against Sexually Transmitted Infections/World Health Organization guideline were evaluated during the clinical examination.[16] Vaginal swab samples were collected for microbiologic analysis and sent to a central laboratory (Ege University Medical Faculty, Department of Microbiology, İzmir, Turkey) for a polymerase chain reaction (PCR) test, Gram staining, and direct microscopic examination. The presence of *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* was evaluated with PCR tests using BD MAX™ Vaginal Panel assays (BD, Sparks, MD 21152-0999 USA). In addition to the Nugent scores, the presence of CVV were evaluated microbiologically in the central laboratory.[17] All microbiological examinations were performed by the same microbiologist who was blinded to the clinical diagnosis. Treatment was initiated immediately after clinical and gynecologic examinations and microbiological results were obtained approximately 3 days after the physical examination. Accordingly, 2 diagnoses were available in this study: the initial clinical diagnosis of the investigator and the laboratory confirmatory diagnosis made according to the results of the microbiologic examinations. Patients were instructed to administer Gynomax® XL vaginal ovule at night, once daily for 3 consecutive days. AEs and compliance to the study treatment were monitored via telephone calls and a patient diary. Similar to many other studies, a follow-up visit was scheduled 10 (+/-5) days after the end of the treatment.[18,19] At the follow-up visit, the patients were examined and the persistence of the clinical findings that were recorded during the baseline visit was evaluated.

Due to the descriptive nature of the study, no formal sample size calculation was performed, and it was concluded that it would be sufficient to enroll a total of 100 patients in the study. Efficacy was evaluated with patients who completed the study in accordance with the protocol whereas safety was evaluated with patients who received at least one dose of the study medication. Data were analyzed using descriptive statistics. The Wilcoxon signed-rank test was used for the comparison of mean baseline and follow-up parameters. McNemar's test was used to compare symptoms/signs recorded at baseline and during the follow-up visit.

RESULTS

Between April and August 2019, a total of 116 patients were enrolled in the study. Eighteen patients did not complete the study according to the protocol. As a result, 98 patients who were eligible according to the inclusion/exclusion criteria, had evaluable efficacy data at baseline and follow-up visits, and completed the study according to the protocol were included in the efficacy analysis. One hundred and 16 patients who received at least one dose of Gynomax® XL were included in the safety analysis.

The mean (±SD) age of the patients was 32.4±7.8 years, and the mean body mass index was 24.8±4.7 (range, 15.1-40.5) kg/m^2. The distribution of the signs and symptoms of the patient group both at baseline and follow-up visits are presented in Table 1. Significant reductions ($p<0.001$) were observed in the frequency and severity of all evaluated symptoms and signs except for vulvar fissuring, genital ulceration, distant skin lesions (satellite lesions), vulvar edema, and strawberry cervix appearance. Investigators' initial clinical diagnoses as well as laboratory diagnoses according to the results of microbiologic examinations are provided in Table 2. For each clinical diagnosis, corresponding laboratory diagnoses and distributions of patients are shown in Table 3.

The primary endpoint of this study was the ratio of patients who had fully recovered according to the clinical and microbiologic findings for each diagnostic criterion. Overall recovery was calculated in all patients regardless of their type of vaginal infection. According to the clinical findings, overall complete

TABLE 1: Clinical signs/symptoms evaluated during the clinical and gynecological examinations and significance of reduction when compared to baseline.

	Baseline[a]		Follow-up[a]		p value[b]
Clinical signs/symptoms evaluated during the clinical and gynecologic examinations	**n**	**%**	**n**	**%**	
Thin, white, homogeneous discharge covering the vagina and vestibule wall	71	72.4	23	23.5	**<0.001**
Offensive fishy odor	50	51.0	1	1.0	**<0.001**
Purulent discharge	62	63.3	8	8.2	**<0.001**
Burning or stinging sensation in the vulva	51	52.0	10	10.2	**<0.001**
Superficial dyspareunia	40	40.8	3	3.1	**<0.001**
Vaginal erythema and edema	41	41.8	3	3.1	**<0.001**
Genital ulceration	3	3.1	0	0.0	NA
Thick, cottage cheese-like vaginal discharge (non-offensive)	43	43.9	8	8.2	**<0.001**
Vulvar pain/itching and erythema	60	61.2	11	11.2	**<0.001**
Vulvar fissuring	6	6.1	1	1.0	0.125
Distant skin lesions (satellite lesions)	0	0.0	0	0.0	NA
Vulvar edema	14	14.3	0	0.0	NA
Frothy and yellow-colored vaginal discharge with offensive odor	43	43.9	7	7.1	**<0.001**
Dysuria	29	29.6	6	6.1	**<0.001**
Discomfort in the lower abdominal area	26	26.5	5	5.1	**<0.001**
Strawberry cervix appearance	0	0.0	0	0.0	NA

[a]Frequency and percentage of patients regardless of severity (mild, moderate, severe) of the symptom; [b]McNemar's test comparing baseline and follow-up visits according to frequencies in each severity group (mild, moderate, severe); NA: Not available.

TABLE 2: Distribution of patients according to the initial clinical diagnosis and the laboratory diagnosis.

	n	%
Initial clinical diagnosis		
Only bacterial vaginosis	24	24.5
Only candidal vulvovaginitis	20	20.4
Only trichomonal vaginitis	1	1.0
Mixed vaginal infection	53	54.1
Total	98	100.0
Laboratory diagnosis		
Bacterial vaginosis	44	44.9
Candidal vulvovaginitis	20	20.4
Mixed vaginal infection	13	13.3
No infection	21	21.4
Total	98	100.0

recovery was observed in 76.5% of the patients. After classification of the patients by infection type, complete recovery was detected in 82.9%, 67.7%, 100.0%, and 77.4% of the patients with BV, CVV, TV, and MVIs, respectively. According to the microbiologic findings, overall complete recovery was observed in 85.7% of the patients. According to the microbiologic evaluations, complete recovery was detected in 93.2%, 85.0%, and 61.5% of the patients with BV, CVV, and MVIs, respectively.

Secondary efficacy endpoints of this study were: (1) the ratio of patients who had partially recovered according to the clinical and laboratory findings for each diagnostic criterion; and (2) the ratio of patients who had not recovered according to the clinical and laboratory findings for each diagnostic criterion. According to the clinical findings, overall partial recovery was observed in 20.4% of the patients. Partial recovery was detected in 14.3%, 29.0%, 0.0%, and 18.9% of the patients with BV, CVV, TV, and MVIs, respectively. According to the microbiologic findings, patients either recovered completely or did not recover at all; therefore, no partial recovery was observed. Considering the overall patient population, 3.1% of the patients did not recover according to the

TABLE 3: Relationship between clinical and laboratory diagnosis.

Clinical diagnosis	Laboratory diagnosis	n	%
Bacterial vaginosis	Bacterial vaginosis	20	57.14
	No infection	8	22.86
	Candidal vulvovaginitis	5	14.29
	Bacterial vaginosis+Candidal vulvovaginitis	1	2.86
	Bacterial vaginosis+Trichomonal vaginitis	1	2.86
	Total	35	100.00
Candidal vulvovaginitis	Candidal vulvovaginitis	14	45.16
	Bacterial vaginosis+Candidal vulvovaginitis	7	22.58
	No infection	6	19.35
	Bacterial vaginosis	4	12.90
	Bacterial vaginosis+Trichomonal vaginitis	NA	NA
	Total	31	100.00
Mixed vaginal infection	Bacterial vaginosis	27	50.94
	No infection	10	18.87
	Candidal vulvovaginitis	9	16.98
	Bacterial vaginosis+Candidal vulvovaginitis	6	11.32
	Bacterial vaginosis+Trichomonal vaginitis	1	1.89
	Total	53	100.00
Trichomonal vaginitis	Candidal vulvovaginitis	1	100.00
	Total	1	100.00
Mixed vaginal infection	Trichomonal vaginitis+Bacterial vaginosis	1	100.00
	Total	1	100.00

NA: Not available.

clinical findings. Considering the type of vaginal infection, the percentage of patients who did not recover according to the clinical findings were 2.9%, 3.2%, 0.0%, and 3.8% in the BV, CVV, TV, and MVI groups, respectively. In terms of laboratory evaluations, 14.3% of the overall women population did not recover. Considering the type of vaginal infection, the percentages of patients who did not recover according to the microbiologic results were 6.8%, 15.0%, and 38.5% in the BV, CVV, and MVI groups, respectively. Recovery percentages according to the clinical and microbiologic evaluations are presented in Table 4 and Figure 1.

The mean vaginal pH values and Nugent scores were significantly reduced in patients following three days of Gynomax® XL treatment (Table 5).

TABLE 4: Recovery according to the clinical and microbiological evaluations.

	Complete recovery		Partial recovery		No recovery		Total	
	n	%	n	%	n	%	n	%
Recovery according to the clinical evaluations								
Overall	75	76.5	20	20.4	3	3.1	98	100.0
Bacterial vaginosis	29	82.9	5	14.3	1	2.9	35	100.0
Candidal vulvovaginitis	21	67.7	9	29.0	1	3.2	31	100.0
Mixed vaginal infection	41	77.4	10	18.9	2	3.8	53	100.0
Recovery according to the microbiological evaluations								
Overall	66	85.7		NA	11	14.3	77	100.0
Bacterial vaginosis	41	93.2		NA	3	6.8	44	100.0
Candidal vulvovaginitis	17	85.0		NA	3	15.0	20	100.0
Mixed vaginal infection	8	61.5		NA	5	38.5	13	100.0

NA: Not available.

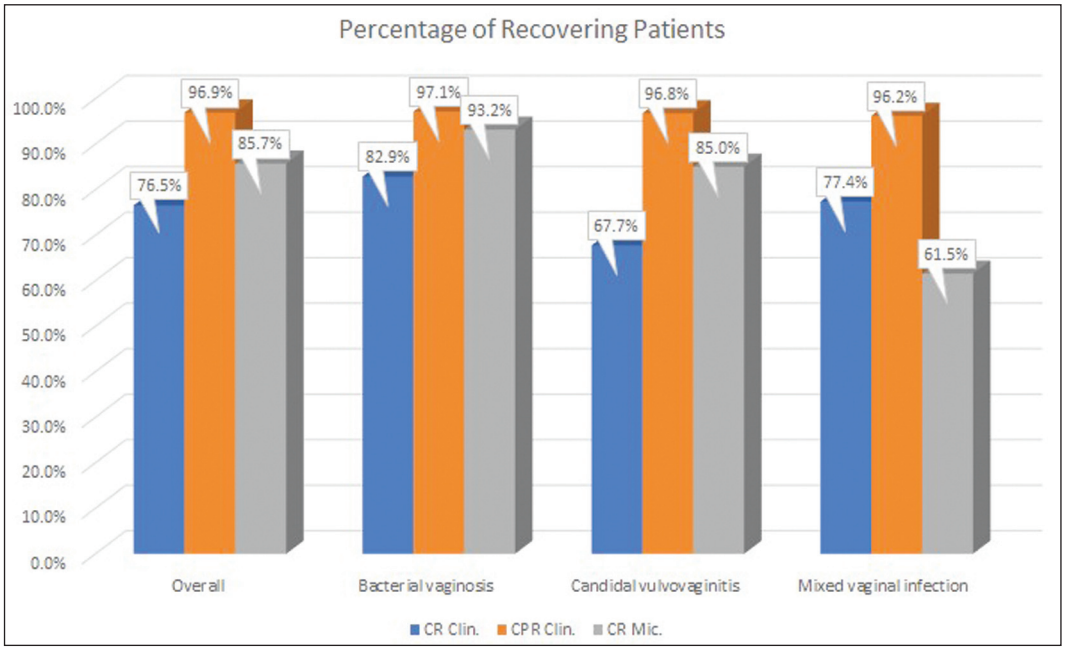

FIGURE 1: Percentage of recovering patients according to clinical and microbiological findings.

CR Clin.: Complete recovery according to the clinical findings; CPR Clin.: Complete or partial recovery according to the clinical findings; CR Mic.: Complete recovery according to the microbiologic results.

TABLE 5: Mean (±SD) pH values and Nugent scores based on laboratory diagnosis at baseline and follow-up visits.

Clinical diagnosis	n	Baseline visit Mean (±SD)	Follow-up visit Mean (±SD)
pH			
Bacterial vaginosis	44	5.74 (±1.41)	4.76 (±1.25)**
Candidal vulvovaginitis	20	5.33 (±1.05)	4.58 (±0.71)*
Mixed vaginal infection	13	5.88 (±1.37)	5.85 (±1.90)
Nugent score			
Bacterial vaginosis	44	8.09 (±1.07)	3.50 (±1.53)**
Candidal vulvovaginitis	20	4.50 (±1.40)	3.25 (±1.25)*
Mixed vaginal infection	13	8.38 (±1.26)	4.38 (±2.29)*

*p<0.05 (Compared with baseline using the Wilcoxon signed-rank test); **p=0.001 (Compared with baseline using the Wilcoxon signed-rank test); SD: Standard deviation.

Safety was evaluated in the safety population, which consisted of 116 patients who received at least one dose of Gynomax® XL. There were no serious AEs or any AEs leading to patient withdrawal during this study. Among the 116 patients, 17 patients (14.6%) experienced 32 AEs. The most frequently reported AEs were gastrointestinal disorders (5.2%), followed by musculoskeletal and connective tissue disorders (4.3%), general disorders and administration site conditions (3.4%), and skin and subcutaneous disorders (3.4%). Most of the AEs were mild in terms of severity and were unlikely related to the study medication. None of the patients discontinued Gynomax® XL treatment temporarily or permanently due to an AE or due to non-tolerability. Gynomax® XL was considered as safe and well tolerated in terms of AEs, and clinical and laboratory evaluations following intravaginal administration for 3 consecutive days.

DISCUSSION

The most common types of vaginitis are BV, CVV, and TV.[1,20] These 3 types of vaginitis usually account for over 90% of all vaginitis cases.[8] Among these three types of vaginal infections, the most frequently observed infection is BV (40% to 50%), followed by CVV (20% to 25%), and TV (15% to 20%).[20] In addition, MVIs caused by more than one agent are usually observed in 15% of patients with vaginitis.[8] In a study recently conducted in the Russian Federation, similar frequencies were observed (52.2% BV, 40.6% CVV and 7.2% MVIs).[19] In our study, according to the investigators' initial clinical diagnoses, most of the patients had MVIs (54.1%), followed by BV (24.5%) and CVV (20.4%) at the baseline visit. One (1.0%) patient was diagnosed as having TV. Although our results have a similar microbiologic diagnosis rate with previously reported data, a much higher rate of MVIs (54%) was diagnosed in the clinical diagnosis.

Compared with initial clinical diagnosis, the microbiologic data obtained from 21 (21.4%) patients resulted with no causative microorganism because not all microbiologic investigations other than for common vaginitis (such as anaerobic causative agents for vaginitis) were performed. Additionally, one patient was clinically diagnosed as having TV, but this clinical diagnosis was not confirmed with the microbiologic test. Although microbiologic tests usually have high sensitivity, in cases where all causatives are not microbiologically evaluated, clinician's diagnosis and laboratory test results may differ as shown in other studies.[21]

In some cases, microbiologic evaluations of vaginal swabs resulted negative for common vaginitis infections. This was an expected outcome because diagnosis of vaginal infections cannot always be established according to the clinical findings alone.[2,3,19] In our study, these incomplete microbiologic diagnoses may be due to evaluation of the only most common three causatives of BV. Since all patients who received initial clinical diagnosis without microbiologic confirmatory results were clinically recovered in the follow-up visit (90.5% complete recovery, 9.5% partial recovery), treatment provided in this study was considered effective for this subgroup of patients.

Gynomax® XL vaginal ovule is the first approved original fixed-dose combination product containing tinidazole, tioconazole, and lidocaine on the market, and this is the second but the largest clinical study with this fixed-dose combination. In order to evaluate our cure rates, the results of similar studies reporting cure rates in BV and CVV were reviewed.

A similar study was conducted in the Russian Federation with Gynomax® XL with the same dosing

regimen and overall recovery was observed at 10 and 30 days after the initiation of treatment. The overall recovery was 80.6% on day 10, and 86.6% on day 30 in that study.[19] Our study results were similar in general; however, the cure rate achieved on the tenth day in our study was slightly higher (96.5% vs 80.6%) than the cure rate achieved on day 10 in the Russian study.

The efficacy of a vaginal pessary (Neo-Penotran®, Exeltis İlaç, İstanbul, Turkey) containing 500 mg metronidazole and 100 mg miconazole nitrate was evaluated in patients with CVV and BV.[22] In our study, slightly higher microbiologic cure rates were obtained in BV (93.2% vs. 86.6%) and CVV (85.0% vs. 81.0%) infections. In a similar study, vaginal pessaries containing 750 mg metronidazole, 200 mg miconazole nitrate, and 100 mg lidocaine were administered for treatment of common vaginal infections.[23] Again, microbiological cure rates of our study are slightly higher both for BV (93.2% vs. 91.7%) and CVV (85.0% vs. 80.0%). Due to the higher cure rates, shorter duration of treatment, and lesser frequency of administration, we consider Gynomax® XL to be a more advantageous treatment.

Centers for Disease Control and Prevention suggest oral or topical agents (e.g. metronidazole, tinidazole, etc.) for treatment of BV and CVV.[24] In general, study results obtained with oral treatments are not superior to topical treatments. In a comparative, prospective, randomized study in patients with BV, the cure rates of a single oral dose of metronidazole (2 g), tinidazole (2 g), secnidazole (2 g), and ornidazole (1.5 g) were compared. During the first week, the cure rate of tinidazole and ornidazole was 100%, and at the fourth week, it was 97.7% for both drugs. Secnidazole had a cure rate of 80.2% at the fourth week. Metronidazole showed a cure rate of 77.9% at the fourth week, which was the lowest cure rate of all four drugs.[25] Following single daily vaginal administration of Gynomax® XL for 3 consecutive days, we achieved similar cure rates in BV with oral tinidazole therapy (100% vs. 93.2%). During the development of Gynomax® XL, tinidazole was preferred instead of metronidazole due to better efficacy.[26] In addition, instead of oral treatment, vaginal administration of tinidazole provides less frequently observed AEs which may be considered as an advantage of Gynomax® XL treatment when compared to oral treatments.[8]

Following multi-day dosing of 2 g oral tinidazole, among 1,765 patients, 13.8% reported AEs. The most common reactions were metallic/bitter taste, nausea, anorexia (gastrointestinal system), and weakness/fatigue/malaise (central nervous system).[27] Although the rate of patients reporting AEs is similar in our study compared with previous studies (13.8% vs. 14.6%), considering the most common AEs such as metallic/bitter taste, nausea, it is observed that these AEs were less frequently reported in our study (metallic/bitter taste 6.3% vs. 0.9%, nausea 4.5% vs. 2.6%). The efficacy and safety of tioconazole and clotrimazole vaginal gel was compared in a prospective clinical study in patients with CVV. Following single-dose vaginal administration of tioconazole vaginal gel, the most frequently reported AEs were pruritis (3.6%), irritation (2.7%), and burning sensation (1.8%). These reactions were mild to moderate in intensity and resolved spontaneously without requiring treatment.[28] In another study conducted in patients with TV and MVIs (n=20), tioconazole was topically administered and only one patient reported mild vaginal burning as an AE.[12] In our study, the same AEs were reported with lower occurrence rates.

In a randomized, controlled trial comparing the efficacy and safety of tinidazole and metronidazole in the treatment of BV, patients received either 2 g tinidazole oral tablets once daily for 2 days, or 500 mg metronidazole oral tablets twice daily for seven days. Even though similar cure rates were obtained with both treatment regimens (approximately 85%), the lesser frequency of administration and shorter duration of treatment may be considered as advantages for tinidazole treatment.[18] In their review, Armstrong and Wilson indicated that tinidazole had a more favorable safety profile when compared with metronidazole due to better gastrointestinal tolerability and less metallic taste. They also mentioned that repeated administrations of metronidazole might be poorly tolerated, and in such cases, tinidazole could be preferred.[29] We consider that the safety profile of our study population is favorable and consistent with previously reported data of oral tinidazole therapy.

From the safety standpoint, most of the AEs reported in our study were mild in terms of severity. The investigators evaluated AEs as being unlikely to be related to the study medication, and none of the patients discontinued Gynomax® XL treatment temporarily or permanently due to any AEs. According to the results of our study we conclude that with intravaginal treatment, we achieved the same success rate as in oral treatments and we observed a favorable safety profile. The safety profile of Gynomax® XL, which is consistent with the current literature, can be considered as the greatest advantage of this treatment.

Intravaginal antibiotic treatments disrupt the domination of pathogens causing BV however these treatments are not designed to restore the lactobacilli.[30] In our study, Gynomax® XL treatment significantly eradicated the pathogens as confirmed by the microbiological results and reduced vaginal pH values, which helps in the restoration of the normal vaginal flora. However, evaluation of vaginal pH on the tenth day of treatment may be a little early because complete restoration of the vaginal flora and domination of lactobacillus species may take longer. Further research may be conducted to evaluate the long-term effects of Gynomax® XL on the restoration of vaginal flora.

We are aware of the possible limitations associated with sample size of this study since no formal sample size calculation was performed while designing the study. In addition, this study was conducted in 3 most populated cities in Turkey however with limited sample size, the data presented in this report may not represent national data homogenously.

In common vaginitis, laboratory diagnosis is not always possible because tests take a long time, and they are not always cost-effective. In such cases, although clinical diagnosis alone is not a definitive diagnosis, use of a combination treatment covering all microorganisms that cause common vaginitis would be a reliable approach.

CONCLUSION

As a result, Gynomax® XL was considered safe, well-tolerated, and highly effective in the treatment of BV, CVV, and MVIs following intravaginal administration for 3 consecutive days.

Source of Finance

Exeltis İlaç, İstanbul, Turkey, provided full financial sponsorship for this study (project code: MON564.13.1) including study medications, patient consultation fees, laboratory payments and investigator payments.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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