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Comparison of a novel treatment protocol with oral fluconazole *vs* probiotic *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14 in the treatment of recurrent vulvovaginal candidiasis

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ABSTRACT

Objective. The recurrence of vulvovaginal candidiasis represents a therapeutic challenge. The aim of this prospective case-control study on a series of women with recurrent vulvovaginal candidiasis (RVVC) was to evaluate the efficacy of a new treatment schedule based on fluconazole 200 mg oral capsules in comparison with oral capsules of *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14.
Patients and Methods. The study was conducted from April 2020 to June 2021 at the Units of Gynecology and Dermatology, Tor Vergata University Hospital, Rome. One hundred and one adult female patients enrolled in the study were divided into two groups: group A treated with 200 mg fluconazole capsules on day 1, 4, 11, 26, then once a month for three months; group B, two oral capsules of *L. rhamnosus* GR-1 and *L. reuteri* RC-14 daily for 15 days/month for three months. Statistical analysis was performed using the Chi-square test. A $p < 0.05$ was considered statistically significant.
Results. A complete clinical response was observed in all 50 patients of the group A at 6 months with no relapse. In the group B, a complete clinical response was observed in 29 patients with ten relapses at 6 months. Itch, leucorrhoea and vulvodynia showed a statistically significant better outcome in the group A (respectively, $p < 0.001$, $p < 0.001$, $p < 0.002$).
Conclusions. The proposed new treatment schedule using fluconazole allows the fungal biofilm to be directed into the different growth stages, with greater efficacy than the administration of probiotics alone.

INTRODUCTION

Vaginal fungal infections are common in the female population and are associated with predisposing factors. Fungal infection of the vulva and vagina is estimated to be the second most common cause of inflammation after bacterial vaginosis [1]. About three-quarters of women of reproductive age have at least one episode of vulvovaginal candidiasis [2, 3]. *Candida albicans* is the most commonly identified pathogen and is responsible for 85 to 90% of all cases. *Candida albicans* is a member of the healthy human microbiota, which asymptomatically colonizes several niches in the body, including, but not limited to, the gastrointestinal tract, the female reproductive tract, the oral cavity and the skin [3]. In immunocompetent individuals, *Candida albicans* is a harmless diner living in harmony with other members of the microbiota. However, alterations in this delicate balance, due to predisposing factors (*e.g.*, menstrual cycles, sexual intercourse, birth control methods, aging, medication, nutritional or hormonal changes and pregnancy), changes the local environment, and pH shifts or dysregulation of the immune system due to infection or immunosuppressive therapy, may allow *Candida albicans* to proliferate rapidly and cause infections [4]. *Candida albicans* forms highly structured biofilms composed of multiple cell types (round yeast cells in the bud, oval pseudo-iphal cells, and elongated hyphatic cells) enclosed in an extracellular matrix [5]. Recurrent vulvovaginal candidiasis (RVVC) treatment is difficult and takes months to achieve a successful clinical response [6].

For the treatment of vaginal candidiasis, the azole group is considered the most effective drug (econazole, clotrimazole, miconazole, ketoconazole, sertaconazole) [6, 7]. Azole compounds are administered locally, using vaginal cream or tablets or suppositories, or orally. Local administration is safe and allows their use during pregnancy [8]. Although various treatments are currently available and effective, the recurrence of candidiasis is common and represents a therapeutic challenge for both gynaecologists and dermatologists. The most commonly used drugs for the treatment of vaginal yeast infections are imidazole derivatives. Fluconazole is a trimidazole with antifungal activity. Currently for the treatment of recalcitrant *Candida albicans* infections, fluconazole 150 mg capsules are administered orally every three days (day 1, 4, 7) followed by a maintenance period in which is administered once a week for six months [6, 7, 9, 10].

As reported in the literature, the intake of lactobacilli reduces the risk of vaginitis, vaginosis and infections of the urogenital system, as it allows rebalancing the intestinal and vaginal flora through the competition of the different administered microorganisms with the pathogenic species, which in many cases appear to be the same saprophytes as Candida [11-13]. In addition to the competition between species, other mechanisms of action to resolve the dysbiosis that underlies RVVC are the stimulation of a correct immune and anti-inflammatory response, and normalization of physiological pH (about 4 in vagina, and between 5 and 7 in intestine). The use of probiotic strains, in particular *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14, proved able to increase the effectiveness of an antifungal pharmaceutical agent in the treatment of RVVC [14].

Further, the importance of a natural approach using probiotics has been successfully tested in different women conditions such as cystitis or menopause [15-17].

The aim of this prospective observational case-control study on a series of women with RVVC was to evaluate the efficacy of a new treatment schedule, based on fluconazole 200 mg oral capsules, administered on days 1, 4, 11, 26, and then once a month for three months, compared with oral capsules of *Lactobacillus rhamnosus* GR-1 (1* 1 × 109 UFC) and *Lactobacillus reuteri* RC-14 (0.5 × 109 UFC), administered twice daily for 15 days/month for three months.

PATIENTS AND METHODS

The study has been conducted at the Unit of Gynecology of Tor Vergata University Hospital, in collaboration with the Unit of Dermatology and Venereology of the same centre, from April 2020 to December 2021. It was a prospective observational case-control study, approved by the local Ethics Committee with the protocol nr. 80/17 and carried out according to the Helsinki Declaration. Written informed consent was obtained from each registered patient. One hundred one adult female Caucasian patients (18 to 56 years of age, mean age: 31 ± 7) referred to the gynaecology clinic, suffering from RVVC, assessed on vaginal swab, were enrolled in the study. The inclusion criteria

were age ≥ 18 years and positive vaginal swab test for *Candida albicans* with recurrent symptomatic disease. The criteria for exclusion were pregnancy and treatment with systemic or local immunosuppressive drugs. Patients were divided into two different treatment groups. In the first group (group A), fluconazole 200 mg oral capsules were given using the following schedule, one tablet on day 1, 4, 11 and 26, followed by one capsule once a month for three months. The second group of patients (group B) was treated with oral capsules of *Lactobacillus rhamnosus* GR-1 (1* 1 × 109 UFC) and *Lactobacillus reuteri* RC-14 (0.5 × 109 UFC), administered twice daily for 15 days/month for three months. Characteristic data of the treated groups (A and B) at baseline (Ti) are showed in **Table 1**. The vaginal swab test was performed at baseline, and at 6 months after the treatment for confirming the effectiveness of the therapy. Itching and vulvodynia were evaluated using the visual analogue scale (VAS) from zero (absence) to 10 (the worst imaginable). The clinical response was classified as complete (complete remission of all signs and symptoms), partial (improvement or partial remission of signs and symptoms), and no response (no change or worsening of signs and symptoms). Itch and leucorrhoea were evaluated at baseline (Ti), and after 6 months (T6) in both groups A and B. The evaluation of vulvodynia was performed at baseline (Ti), and after one (T1) and 6 months (T6). Adverse events were recorded.

Statistical analysis

All data were initially entered into an Excel spreadsheet (Microsoft, Redmond, Washington-United States), and the analysis was performed using the Statistical Package for the Social Sciences Windows, version 26.0 (SPSS, Chicago, Illinois, USA). Descriptive statistics consisted of the mean ± standard deviation (mean ± SD) for parameter with normal distributions or median and range (min; max) for

Table 1. *Characteristic data of the treated groups (A, B) at baseline (Ti).*

Group (n patients)	P-value A *vs* B	
A (50)	Treatment schedule Fluconazole 200 mg capsule On day 1, 4, 11, 26, and once a month for 3 months Demographics data (M ± S) Age: 32 ± 8 ys BMI: 23.46 ± 4.63 Kg/m^2 Comorbidities n pts (%) Smoke: 13 pts (26.0%) Chronic constipation: 20 pts (40.0%) Contraception n pts (**%**) OC: 18 pts (36.0%) Condom: 25 pts (50.0%)	Age: p = 0.694^ BMI: p = 0.258^ Smoke: p = 0.420* Chronic constipation: p = 0.663* OC: p = 0.272* Condom: p = 0.197*
B (51)	Treatment schedule 2 capsules (*L. rhamnosus* GR-1 and *L. reuteri* RC- 14) per day for 15 days/month for 3 months Demographics data (M ± S) Age: 31 ± 7 ys BMI: 22.50 ± 3.76 Kg/m^2 Comorbidities n pts (%) Smoke: 17 pts (33.3%) Chronic constipation: 24 pts (47.1%) Contraception n pts (%) OC: 13 pts (25.5%) Condom: 32 pts (62.7%)	

^Anova test one-way; *Chi-square test; OC: oral contraceptive.

variables with non-normal distributions, while the occurrences values are reported as percentages. Comparisons of normal data between treatment groups and between pre and post treatment were conducted with Anova one-way or Anova for measures repeated, while dichotomous occurrences were evaluated with Chi-squared test. A P-value < 0.05 was considered statistically significant.

RESULTS

All 101 female patients completed the study. Vaginal swab tests at baseline demonstrated the presence of *Candida albicans* in the totality of the patients. Vaginal discharge associated with vulvodynia was initially present in all 101 (100%) patients recruited in the study. The median itch and vulvodynia VAS score at the time of the first visit was nine for both groups. Follow up visits were scheduled at 1 and 6 months from beginning of therapy. An improvement of all symptoms was observed significantly more in group A than in group B (**Table 2**). **Figure 1a** shows the decrease of itch score (VAS) in groups A and B pre and after treatment (6 months). It was significantly lower in group A. The percentages of patients with leucorrhoea in groups A and B pre and after treatment (6 months) are showed in **Figure 1b**. At 6 months, none of the patients in group A presented leucorrhoea against 41.2% of the patients in group B. **Figure 1c** shows the percentages of patients with vulvodynia in groups A and B, at one and 6 months from the beginning of the treatment. At 6 months, 12% of the patients in group A complained of vulvodynia against 39.2% of the patients in group B. None of the 101 patients in the two groups of treatments reported side effects during the period of treatment, and none needed hospitalization.

DISCUSSION

Candida albicans is responsible for 85-90% of all vulvovaginitis, and affects women of all ages. Although various treatments are currently available and effective, the recurrence of vulvovaginal candidiasis is common, and represents a therapeutic challenge for both gynaecologists and dermatologists. Recurrent vulvovaginal candidiasis can have a significant effect on the quality of life. The treat-

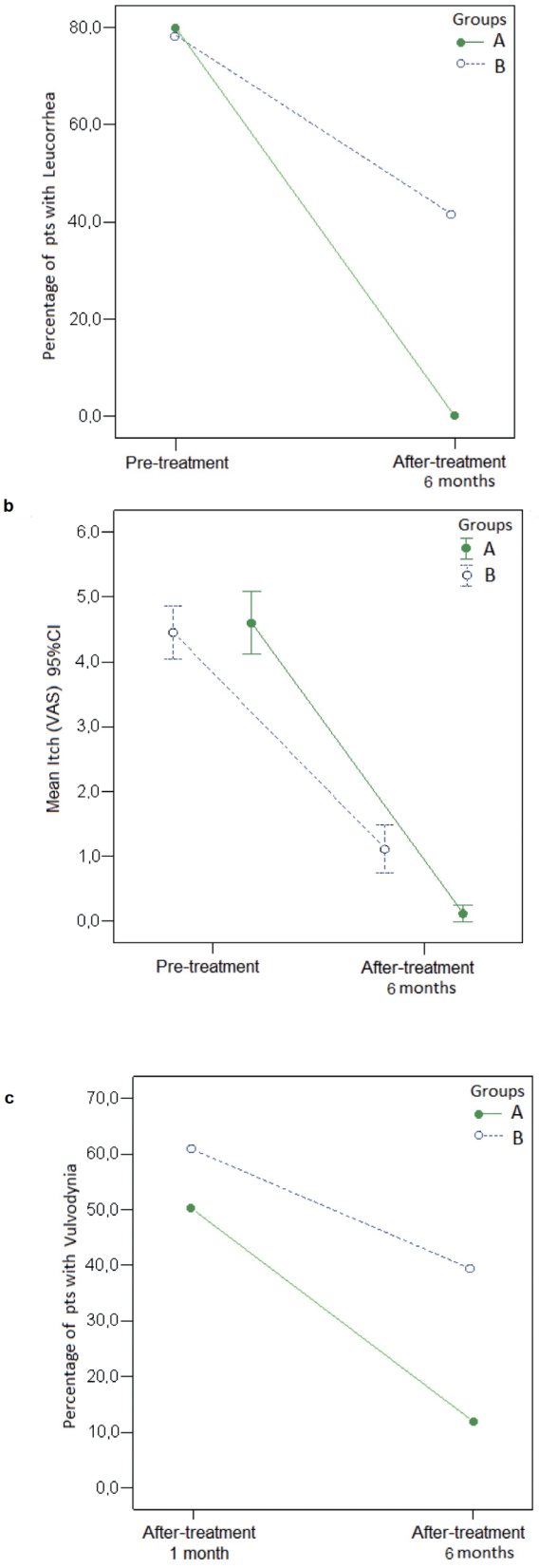

Figure 1. ***(a)*** *Difference of itch score (VAS) in groups A and B pre and after treatment (6 months);* ***(b)*** *Percentage of patients with leucorrhea in groups A and B pre and after treatment (6 months);* ***(c)*** *Percentage of patients with vulvodynia in groups A and B after treatment (1 and 6 months).*

(a) *Percentage of patients with leucorrhea in groups A and B pre and after treatment (6 months) 39 × 40 mm (300 × 300 DPI);* ***(c)*** *Percentage of patients with vulvodynia in groups A and B after treatment (1 and 6 months) 39 × 40 mm (300 × 300 DPI).*

Table 2. *Symptoms in groups A and B at baseline (Ti) and at 6 months (T6).*

Group (n patients)	Itch (VAS) (mean ± SD)		Leucorrhoea n pts (%)		Vulvodynia n pts (%)	
	Ti Pre-treatment	T6 6 months	Ti Pre-treatment	T6 6 months	Ti Pre-treatment	T6 6 months
A (50)	(4.6 ± 1.6)	(0.1 ± 0.4)	40 pts (80.0%)	0 pts (0.0%)	25 pts (50.0%)	6 pts (12.0%)
B (51)	(4.5 ± 1.4)	(1.1 ± 1.3)	40 pts (78.4%)	21 pts (41.2%)	31 pts (60.8%)	20 pts (39.2%)
P-value A *vs* B	p = 0.633^	**p = 0.002**^	p = 0.846*	**p = 0.001***	p = 0.276*	**p = 0.002***

^Test Anova for repeated measures; *Chi-square test.

ment is based on the administration of topical and systemic antifungal drugs, but existing treatment schedules are often unsatisfactory [5, 7, 9].

Azole compounds are the first choice for the treatment of uncomplicated-candida vulvovaginitis [7, 18]. In some studies, it has been reported that topical sertaconazole is the most effective anti-yeast drug for controlling inflammation and itching due to *Candida albicans* infection [19-21]. In recent years, imidazole derivatives have become the most commonly used drugs to treat vaginal yeast infections [22-25].

The use of probiotic strains, in particular *Lactobacillus rhamnosus* GR-1 and *Lactobacillus reuteri* RC-14, proved able to increase the effectiveness of an antifungal pharmaceutical agent in the treatment of vulvovaginal candidiasis. In this regard, a Brazilian study [14] conducted on a cohort of 55 patients, randomized into two groups, positive for Candida spp. (*C. albicans* in 90% of cases) and with at least one characteristic symptom (leucorrhoea, itching, burning, dysuria, dysuria) has validated this hypothesis. In fact, in patients treated with fluconazole 150 mg single-dose therapy combined with probiotic at a dose of 2 billion per day for 4 weeks, greater efficacy was demonstrated than in patients receiving fluconazole monotherapy, resulting in a significant reduction of associated symptoms (10.3% *vs* 34.6%; p = 0.03), and a significant reduction of candida in culture (10.3% *vs* 38.5%; p = 0.014). The same combination therapy was then implemented in the treatment of a subgroup of patients with a history of recurrent vulvovaginal candidiasis, once again proving effective in negativizing vaginal swab (80.0% *vs* 18.2%) and in improving symptomatology.

Likewise, Witt *et al*. [25]. found that adding *Lactobacillus gasseri* to maintenance itraconazole therapy provided additional benefit in achieving a culture-negative status within 12 months compared to itraconazole alone. Similarly, Pendharkar *et al.* [26]. found that adding a vaginal probiotic containing *Lactobacillus rhamnosus* and *Lactobacillus gasseri* to maintenance fluconazole therapy significantly affected the 6-month or 12-month cure rate of patients with RVVC.

In our study, fluconazole was administered to patients with RVVC using a different treatment regimen compared to the classical regimen. Fluconazole 200 mg oral capsules were administered discontinuously to follow the biorhythm of *Candida albicans*, and to target not only the hyphale, but also vegetative forms of fungi [27]. This new treatment showed to be safe and free of side effects.

In addition, the new dosage has shown a powerful activity and greater efficacy than the daily administration of probiotics, as demonstrated by the improved outcome of patients treated with the new protocol.

We have hypothesized that the increased efficacy of this new schedule of fluconazole can be attributed to the "its intermittent administration", by inhibiting the passage of *Candida albicans* from the hypha form to the spore form (defined as *C. albicans* biorhythm) [27]. In fact, it is known that alkaline pH and temperature above 37 °C facilitate the switching of *C. albicans* to the more virulent (hyphal) or resistant (spore) forms [28].

In one study, fluconazole 200 mg oral capsules have already been administered to patients with RVVC, but at greater intervals together with a probiotic, showing 15.6% of recurrence rate during therapy and 9.8% of relapses during follow-up [11]. On the contrary, with our innovative regimen schedule, patients treated unsuccessfully for years and with chronic relapsing infections achieved a complete response without relapse at six months since the end of therapy. Moreover, it is worth noting that the shorter treatment schedule, as long as the reduced number of capsules administered, has a positive reflection on both quality of women life and cost savings compared to probiotics.

However, one limitation of our study is the small number of patients enrolled. It is advisable that in the future more patients will be enrolled in a multicentre study to further validate the results of our study.

CONCLUSIONS

In conclusion, the present study suggests that a new regimen schedule of fluconazole 200 mg oral capsules is effective in the treatment of RCCV, probably by targeting the fungal biorhythm.

COMPLIANCE WITH ETHICAL STANDARDS

Authors contribution

All authors: Conceptualization, design, formal analysis, data interpretation, writing – original draft, writing review and editing.

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None.

Study registration

N/A.

Disclosure of interests

The authors declare that they have no conflict of interests.

Ethical approval

IRB approval was obtained by the Fonadazione Policlinico Tor Vergata Ethical Committee, before to start (protocol nr. 80/17).

Informed consent

Each patient enrolled in this study gave informed consent to participate in the study and to allow data collection.

Data sharing

Data are available under reasonable request to the corresponding author.

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