

## Clinical Study

# An Evaluation of Theraphy with Fluconazole 150 mg Tablets Compared to Fluconazole 150 mg Tablets Plus Dermoxen Lenitiva Cream in The Time to Reduce Simptomatology in Women with Vulvovaginal Candidiasis

Davide Carati<sup>1,\*</sup>, Valentina Russo<sup>1</sup>, Marcello Guido<sup>2</sup>, Antonella Zizza<sup>3</sup>, Marcella Megha<sup>4</sup>, Malvasi Antonio<sup>5</sup>, Andrea Tinelli<sup>6</sup>

<sup>1</sup>Research & development department, Ekuberg Pharma srl, Martano (LE), Italy

<sup>2</sup>Laboratory of Hygiene, Department of Biological and Environmental Sciences and Technologies, Faculty of Sciences, University of Salento, Lecce, Italy

<sup>3</sup>Institute of Clinical Physiology, National Research Council, Lecce, Italy

<sup>4</sup>Laboratory of Clinical Pathology, Poliambulatory "Cittadella della salute" Lecce, Italy

<sup>5</sup>Department of Obstetrics and Gynaecology, Santa Maria Hospital, Bari, Italy

<sup>6</sup>Department of Obstetrics and Gynecology, Vito Fazzi Hospital, Lecce, Italy

\*Corresponding Author: Davide Carati; email: davide.carati@ekubergpharma.com

Received 23 January 2013; Accepted 4 April 2014

Academic Editor: Osama Ibrahim Azawi

Copyright © 2014 Davide Carati et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

**Abstract.** *Aim of the study.* Authors investigated first of all the time to onset of first relief of symptoms. Secondary measures included the time to overall relief of symptoms and the reoccurrence rate over the first 45 days after the first visit. *Methods.* A randomized, open-label, parallel study evaluated 47 women with moderate to severe symptoms of Vulvo Vaginal Candidiasis (VVC). Patients were divided into two groups of treatment: group 1 followed a therapy with Fluconazole 150 mg tablets, while group 2 had a therapy based on Fluconazole 150 mg tablets coadjuvated by Dermoxen Lenitiva cream. *Results.* The time at which 50% of patients experienced first relief of symptoms was 24.6 hours for Group 1, while for Group 2 it was 12.4 hours ( $P < 0.05$ ). There were significant differences between the two groups in respect to the time of first relief of symptoms and reoccurrence of infection within 45 days of treatment. *Conclusions.* Combined treatment with Fluconazole 150 mg tablets and by Dermoxen Lenitiva cream provides statistically significant improvement in the time of first relief of symptoms, complete relief of symptoms and relapse time in the treatment of VVC compared to fluconazole 150 mg tablets only.

**Keywords:** Fluconazole, Dermoxen, vulvovaginal candidiasis, vaginitis

## 1. Introduction

1 Recurrent vulvovaginal candidiasis (RVVC) is a debilitating chronic infectious condition. It is defined as four or more acute inflammatory episodes of Vulvo Vaginal Candidosis (VVC), also known as vaginal yeast infection, within a year [1, 2]. The *Candida albicans* spp. has been known to be

the main responsible organism for RVVC, accounting for 80%–85% of cases. The other cases are due to non-*albicans* species, with *C. glabrata* being the most common. Its frequency has nearly doubled over the last ten years, and it has been shown to account for 5%–15% of RVVC [3–5]. Other non-*albicans* species also include *C. tropicalis* (< 5%) and *C. krusei* (about 1%) [6]. It has been estimated that 75% of

4

all women will experience at least one episode of VVC, and approximately 40% to 50% reporting a reoccurrence during their lifetime [7]. The main symptoms of yeast infection are inflammation, itching, an abnormal vaginal discharge and painful sexual intercourse and urination [8–11]. All these symptoms often cause severe discomfort, reducing quality of life of women and their partner. Acute inflammatory episodes are usually treated with antifungal drugs of the azole class. They are effective in clearing the acute infection, but they are unable to prevent recurrences, which occur on average after a few months only. Vulvovaginal candidiasis has been associated with considerable direct and indirect economic costs [12], enhanced susceptibility to HIV infection [13], and it is being investigated for a potential relationship with preterm birth [14]. Fluconazole is the only orally available imidazole with approved labeling specific for the treatment of VVC. The recommended therapy is a single 150 mg oral tablet. Many clinical studies have compared a single fluconazole 150 mg oral tablet with a number of different antifungal vaginal topical and suppository preparations. Review of these studies suggests that the overall cure rate with fluconazole 150 mg tablets is similar to that seen with other preparations [15–23]. Moreover Dermoxen Lenitiva cream, a topical formulation based on natural actives, was found to be active against itching [24], often present in women suffering from VVC, and useful to improve intimate comfort and well-being during sexual intercourse.

The purpose of this study was to compare the time of first relief of symptoms due to VVC, evaluating the results of two study groups: group 1 followed a therapy with Fluconazole 150 mg tablets while group 2 had a therapy based on Fluconazole 150 mg tablets plus Dermoxen Lenitiva, a soothing intimate cream produced by Ekuberg Pharma srl (Martano, Lecce- Italy). Moreover, the time for complete relief of symptoms and reoccurrence rate were evaluated, following up patients for 45 days after the end of treatment.

## 2. Materials and Methods

Authors developed a pilot, open-label, randomized study, conducted according to Declaration of Helsinki and approved by an Institutional review Board. Before to start, the protocol and informed consent were reviewed, approved and signed by the patients. Authors enrolled, from July 2013 to November 2013, 47 women who had symptoms of VVC, attending the Department of Gynaecology and Obstetrics of University affiliated Hospital “Vito Fazzi” (Lecce, Italy). Confirmation of current VVC infection was made by use of KOH wet mount preparation, pelvic examination and patient’s reporting of signs and symptoms. The exclusion criteria for such study were: patients suspected of having a concurrent vaginal infection (i.e., bacterial vaginosis, trichomoniasis, herpetic lesions); women with menstruation or women who know menstrual cycle comes within two days; patients with a history of use of intravaginal or systemic antifungal medication

or other intravaginal products (spermicide, douche, spray, gel, cream); women with a medical history of allergies or intolerance to any of the active or non-active ingredients of the study formulations. The symptomatology was evaluated using a scale from 0 (no symptoms) to 10 (severe symptoms) for itching, redness, burning and dryness. Details of last sexual intercourse, last menstrual period, method of contraception, recent treatment, parity, contact’s symptoms and relevant past history were all recorded. After diagnosis by microscopy, the patients were treated randomly with two types of treatment: Group I ( $N = 24$ ) was treated with Fluconazole 150 mg tablets (one tablet per day, for two weeks), Group II ( $N = 23$ ) with a therapy based on Fluconazole 150 mg tablets plus Dermoxen Lenitiva cream (one tablet and one application of cream per day, for two weeks). Patients were recommended to record the time of dosing. The main indication was to follow the treatment in the early afternoon for a better evaluation of first relief of symptoms. Patients were given a personal diary in which they were requested to record the date and time they first started to feel relief of symptoms, and the date and time they had complete relief of symptoms. In this diary patients had to notice any adverse events or concomitant medications. Seven days after the end of the treatment, patients were required to return to hospital for a follow-up visit, during which the investigators checked the diary. 45 days after the end of the treatment, patients were required to return another time to hospital to investigate any case of relapse. The first outcome of the study was the time of first relief of symptoms. The second outcome of the study was the evaluation of complete relief of symptoms and of any case of relapse, and their time of appearance.

*2.1. Statistical analysis.* Two independent reviewers collected, reported and classified data. Baseline demographics (age, number of episodes of VVC in the previous 12 months and severity score) were tabulated and compared using descriptive statistics. Time of first relief of symptoms for each patient was calculated using the relative dosing time and the time reported for first relief of symptoms by each patient. Analysis of these data was performed using Kaplan–Meier estimates and 95% Confidence Interval analysis.  $P$  values less than 0.05 were considered statistically significant.

## 3. Results

In this pilot study, 47 women with recognized VVC were treated with two different protocols and included in two groups: Group I ( $N = 24$ ) and Group II ( $N = 23$ ). A total of 77 patients (33 in group I and 44 in Group II) were eligible for inclusion during first visit; 30 women were excluded according to exclusion criteria (9 in Group I and 21 in Group II). The analysis of demographic data was similar between the two groups (Table 1).

Table 1: Demographic data.

	Group I (N = 24)	Group II (N = 23)	P
Age (mean $\pm$ SD)	34.4 $\pm$ 6.6	34.1 $\pm$ 8.1	0.2540
Parity (mean $\pm$ SD)	1.1 $\pm$ 1.0	1.2 $\pm$ 1.0	0.6430

Both forms of treatment were effective in reducing the signs and symptoms of vaginal candidiasis. All patients in both groups had not registered any adverse events in their diary.

In Table 2 the percentage of patients who recorded first symptoms relief within the first 48 hours is reported. Patients of Group II experienced first relief of symptoms with a higher percentage in comparison with those of Group I at all time points. Fifty percent of patients of Group I experienced first symptom relief within 24.6 hours versus 12.4 of Group II ( $P < 0.05$ ). The median time for total relief was 77.3 hours for Group I and 64.3 for Group II ( $P < 0.05$ ). Evaluating patients of both groups after 45 days from the end of the treatment, a total of 5 patients (20.83%) of Group I experienced a reoccurrence of VVC, versus one patient (4.34%) of Group II ( $P < 0.05$ ).

#### 4. Discussion

This study involved 47 women with recognized VVC, treated with two different protocols and included in two groups: Group I (N = 24) and Group II (N = 23). Both proposed treatments registered an improvement in vaginal symptoms. Combined treatment with Fluconazole 150 mg tablets plus Dermoxen Lenitiva cream (one tablet and one application of cream per day, for two weeks) showed a significant improvement compared to the treatment with Fluconazole 150 mg tablets only, about time of first relief of symptoms of VVC. In fact, fifty percent of patients of Group II experienced first relief of symptoms after 12.4 hours versus 24.5 hours of Group I. It has been estimated that 24 hours is a reasonable period of time in order to evaluate general effectiveness of therapy for VVC. For Group I, 49 % experienced first symptom relief after 24 hours, versus 74.4% for Group II ( $P < 0.05$ ). This is an important result coming out from the study, because it suggests that a combined "oral and topical" treatment is more effective in relieving symptoms of VVC than oral or topical treatment only. Total relief was achieved after 77.3 hours for Group I and 64.3 for Group II. No adverse events were registered in both groups. In particular, in this study the oral treatment was administered to defeat the infection, using fluconazole, because the main objective of any therapy for the treatment of vaginal candidiasis is the eradication of the infecting organism; while the topical treatment was specifically addressed to reduce the symptomatology regarding itching, redness, burning of

Table 2: Time (hours) of first symptom relief.

Hours after dosing	Group I Cumulative % (N = 24)	Group II Cumulative % (N = 23)	P value (*statistically significant)
2	2.9	11.7	$P < 0.05^*$
4	9.1	22.3	$P < 0.05^*$
6	12.5	27.0	$P < 0.05^*$
8	19.2	34.9	$P < 0.05^*$
10	24.0	45.2	$P < 0.05^*$
12	24.0	48.3	$P < 0.05^*$
14	32.8	57.1	$P < 0.05^*$
16	35.1	57.1	$P < 0.05^*$
18	39.4	64.6	$P < 0.05^*$
20	44.4	64.6	$P < 0.05^*$
22	46.7	69.0	$P < 0.05^*$
24	49.0	74.4	$P < 0.05^*$
26	51.1	77.7	$P < 0.05^*$
28	51.1	80.0	$P < 0.05^*$
30	55.6	80.0	$P < 0.05^*$
32	61.5	82.9	$P < 0.05^*$
34	61.5	82.9	$P < 0.05^*$
36	69.8	82.9	$P < 0.05^*$
38	76.0	82.9	$P < 0.05$
40	78.0	85.6	$P < 0.05$
42	81.8	90.4	$P < 0.05^*$
44	85.9	92.0	$P < 0.05$
46	88.0	93.6	$P < 0.05$
48	88.0	95.0	$P < 0.05$

external intimate area in terms of time. Another outcome of this study was to evaluate the reoccurrence time, monitoring patients of both groups for 45 days from the first visit: a total of 5 patients (20.83%) of Group I experienced a reoccurrence of VVC, versus one patient (4.34%) of Group II ( $P < 0.05$ ). This is another important result, which needs better investigation in order to understand if and how Dermoxen Lenitiva cream could have a coadjuvant action against yeast (action not presented by the product). Definitely, combined treatment with Fluconazole 150 mg tablets plus Dermoxen Lenitiva cream (one tablet and one application of cream per day, for two weeks) more rapidly achieves first relief of symptoms of VVC, compared to Fluconazole 150 mg tablets only, reducing cases of RVVC.

#### 5. Conclusion

Combined treatment with Fluconazole and Dermoxen Lenitiva cream should be considered as an important first line therapy in patients presenting the signs and symptoms of VVC and RVVC. A trial involving more patients and more outcomes, may guarantee a better investigation of this

finding, taking care of extending the time of follow up to 90 days.

## References

- [1] P.-A. Mårdh, A. G. Rodrigues, M. Genç, N. Novikova, J. Martinez-De-Oliveira, and S. Guaschino, Facts and myths on recurrent vulvovaginal candidosis—a review on epidemiology, clinical manifestations, diagnosis, pathogenesis and therapy,, **13**, no. 8, 522–539, (2002).
- [2] G. G. G. Donders, G. Bellen, and W. Mendling, Management of recurrent vulvo-vaginal candidosis as a chronic illness,, **70**, no. 4, 306–321, (2010).
- [3] R. Buitrón García-Figueroa, J. Araiza-Santibáñez, E. Basurto-Kuba, and A. Bonifaz-Trujillo, Candida glabrata: an emergent opportunist in vulvovaginitis,, **77**, no. 6, 423–427, (2009).
- [4] J. D. Sobel, Vaginitis,, **337**, 1896–1903, (1997).
- [5] J. Ferrer, Vaginal candidosis: epidemiological and etiological factors,, **71**, supplement 1, 21–27, (2000).
- [6] S. Singh, J. D. Sobel, P. Bhargava, D. Boikov, and J. A. Vazquez, Vaginitis due to Candida krusei: epidemiology, clinical aspects, and therapy,, **35**, no. 9, 1066–1070, (2002).
- [7] J. D. Sobel, Candidal vulvovaginitis,, **36**, no. 1, 153–165, (1993).
- [8] J. D. Sobel, Epidemiology and pathogenesis of recurrent vulvovaginal candidiasis,, **152**, no. 7, 924–935, (1985).
- [9] B. J. Horowitz, D. Giaquinta, and S. Ito, Evolving pathogens in vulvovaginal candidiasis: implications for patient care,, **32**, no. 3, 248–255, (1992).
- [10] J. D. Sobel, Vaginitis,, **337**, 1896–1903, (1997).
- [11] B. Foxman, R. Barlow, H. D'Arcy, B. Gillespie, and J. D. Sobel, Urinary tract infection: self-reported incidence and associated costs,, **10**, no. 8, 509–515, (2000).
- [12] B. Foxman, R. Barlow, H. D'Arcy, B. Gillespie, and J. D. Sobel, Candida vaginitis: self-reported incidence and associated costs,, **27**, no. 4, 230–235, (2000).
- [13] J.-A. Røttingen, W. D. Cameron, and G. P. Garnett, A systematic review of the epidemiologic interactions between classic sexually transmitted diseases and HIV: how much really is known?, **28**, no. 10, 579–597, (2001).
- [14] C. L. Roberts, J. M. Morris, K. R. Rickard, W. B. Giles, J. M. Simpson, G. Kotsiou, and J. R. Bowen, Protocol for a randomised controlled trial of treatment of asymptomatic candidiasis for the prevention of preterm birth,, **11**, article 19, (2011).
- [15] P. O-Prasertsawat and A. Bourlert, Comparative study of fluconazole and clotrimazole for the treatment of vulvovaginal candidiasis,, **22**, no. 4, 228–230, (1995).
- [16] G. E. Stein, S. Christensen, and N. Mummaw, Comparative study of fluconazole and clotrimazole in the treatment of vulvovaginal candidiasis,, **25**, no. 6, 582–585, (1991).
- [17] J. D. Sobel, D. Brooker, G. E. Stein, J. L. Thomason, D. P. Wermeling, B. Bradley, and L. Weinstein, Single oral dose fluconazole compared with conventional clotrimazole topical therapy of Candida vaginitis,, **172**, no. 4 I, 1263–1268, (1995).
- [18] E. Kutzer, R. Oittner, S. Leodolter, and K. W. Brammer, A comparison of fluconazole and ketoconazole in the oral treatment of vaginal candidiasis; report of a double-blind multicentre trial,, **29**, no. 4, 305–313, (1988).
- [19] C. De Punzio, P. Garutti, G. Mollica, C. Nappi, R. Piccoli, and A. R. Genazzani, Fluconazole 150 mg single dose versus itraconazole 200 mg per day for 3 days in the treatment of acute vaginal candidiasis: a double-blind randomized study,, **106**, no. 2, 193–197, (2003).
- [20] M. B. Slavin, G. I. Benrubi, R. Parker, C. R. Griffin, and M. J. Magee, Single dose oral fluconazole vs intravaginal terconazole in treatment of Candida vaginitis. Comparison and pilot study,, **79**, no. 10, 693–696, (1992).
- [21] S. Osser, A. Haglund, and L. Westrom, Treatment of candidal vaginitis. A prospective randomized investigator-blind multicenter study comparing topically applied econazole with oral fluconazole,, **70**, no. 1, 73–78, (1991).
- [22] R. E. Herzog and E. B. Ansmann, Treatment of vaginal candidosis with fluconazole,, **32**, no. 4, 204–208, (1989).
- [23] D. A. Edelman and S. Grant, One-day therapy for vaginal candidiasis: a review,, **44**, no. 6, 543–547, (1999).
- [24] D. Carati, M. Guido, A. Malvasi, A. Zizza, and A. Tinelli, Efficacy of a Dermoxen lenitiva for pruritus genitalis in a randomized, double blind trial,, **17**, no. 19, 2668–2674, (2013).

## Comments

1. We changed the affiliation reference of “Andrea Tinelli” to be “6” instead of “5”. Please check.
2. We changed “p” to “P”. Please check throughout.
3. We split reference “4” to “4 and 5”. Please check.
4. We split reference “9” to “10 and 11”. Please check.