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Clinical Evaluation of the Efficacy and Safety of a Medical Vaginal Device Containing Rigenase® for the Treatment of Vaginosis: A Randomized Study

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Abstract

Background: Vaginitis is an inflammatory process involving the vagina, expanding often to the contiguous anatomical structures (cervix and vulva). From an etiological point of view, there are mainly two types of vaginitis: specific vaginitis (due to pathogenic microorganisms) and non-specific vaginitis (also defined vaginosis), usually caused by an alteration (disruption) of the normal vaginal microflora, usually represented by the presence of Lactobacilli due to opportunist bacteria proliferation. Whereby, the first line therapeutic approach for vaginosis (which is frequently subject to self-medication) should be focused on rebalancing the flora and not on antimicrobials, reserving the latter to persistent cases that are properly characterized by appropriate microbiological tests. A new medical device is available in different formulations for the local treatment of vaginitis and, in addition, of irritative-dystrophic states of the vaginal area.

Methods: In a randomized (kind of the device used), parallel-groups, single-centered, uncontrolled design clinical study, 75 Caucasian female outpatients suffering from vaginosis were treated with the new vaginal medical device (cream, vaginal suppository, vaginal solution, gel, and foam; n = 15 in each group) for 6 days. Before (V1) and at the end of the treatment period (V2), the presence and intensity of pain, burning, itch, dry vagina sense, dyspareunia, dysuria, vaginal discharge, and vulvovaginal erythema were checked. Signs and symptoms were quantified according to the scale: absent = 0, mild = 1, moderate = 2 and severe = 3. The overall symptoms were summarized according to the total symptoms score (TSS), defined as the sum of scores of all signs and symptoms.

Results: The analysis conducted on the TSS for the intention-to-treat (ITT) population showed a statistically significant improvement of symptoms in all treatment groups ($P < 0.001$), with an average reduction of the initial TSS similar in the different groups and ranging between 73% and 80% (with a V2/V1 ratio of 0.27 and 0.20, respectively). No clinically significant differences were observed between the different preparation used. At the starting visit, the most common signs and symptoms were burning, leukorrhea and vulvo-vaginal erythema, each present in 62/75 patients (82.7). All signs and symptoms were significantly regressed or disappeared at the final visit in most of the cases; the improvement score was statistically significant ($P < 0.05$) when analyzing the total of patients, and often it resulted in a significant difference in the individual treatment groups as well, except when only a few patients had a sign/symptom at baseline. None of patients discontinued the application of the device before the schedule period. Adverse events were detected in none of the patients studied.

Conclusions: The medical device in vaginal formulations appears to be effective and safe for the local treatment of moderate-mild inflammatory-dystrophic gynecological diseases.

Keywords: Vaginitis; Bacterial vaginosis; Vaginosis treatment; Rigenase®

Introduction

Vaginitis is an inflammatory process involving the vagina, expanding often to the contiguous anatomical structures (cervix and vulva). This is a very common gynecological disease [1] and it is so frequent that virtually every woman in adulthood has been affected at least once [2]. From an etiological point of view, there are mainly two types of vaginitis: specific vaginitis and non-specific vaginitis (also defined vaginosis), with the latter being the most prevalent [3]. Specific vaginitis are due to local infection by pathogenic microorganisms (bacteria, fungi and protozoa such as chlamydia, candida, and trichomonas); non-specific vaginitis are usually caused by an alteration (disruption) of the normal vaginal microflora, usually represented by the presence of Lactobacilli [4], due to opportunist bacteria proliferation. Causes include the treatment with oral estroprogestinics, pregnancy, use of tight and/or made in synthetic fibers undergarments, therapy with antibiotics, stress conditions, and so on [5]. The therapy for specific vaginitis rest on specific drugs, depending on the etiology (e.g. metronidazole for trichomoniasis), while the treatment for the vaginosis should be focused in restoring the local physiological homeostasis. Never-

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Table 1. Demographic and Somatic Characteristics of the Patients at the Entry (Mean Values ± SD)

	Cream	Vaginal suppository	Vaginal solution	Gel	Foam	Total
n	15	15	15	15	15	75
Age (years)	38 ± 13	38 ± 14	35 ± 10	45 ± 11	37 ± 12	39 ± 12
Weight (kg)	67 ± 14	69 ± 11	63 ± 11	63 ± 9	66 ± 16	65 ± 12
Height (cm)	164 ± 8	161 ± 6	161 ± 6	160 ± 7	162 ± 7	162 ± 7
BMI (kg/cm^2)	25 ± 5	27 ± 4	24 ± 4	25 ± 3	25 ± 6	25 ± 5

theless, it has to be noted that, except in clearly defined cases, such as candida infections, the initial clinical picture of the two types of vaginitis is virtually the same (presence of symptoms such as local itching and burning, leukorrhea, dysuria, and dyspareunia). Whereby, the first line therapeutic approach, which is frequently subject to self-medication [6], should be focused on rebalancing the flora and not on antimicrobials, reserving the latter to persistent cases that are properly characterized by appropriate microbiological tests. A new medical device (Damor Pharmaceuticals, Naples, Italy) is available in different formulations for the local treatment of vaginitis and, in addition, of irritative-dystrophic states of the vaginal area.

Depending on the pharmaceutical forms, several components are present and together they exert a cleansing, refreshing and lenitive action, and in addition, promote the tissue repairing and the cellular microenvironment recovery by acting as mucosal protection elements. These properties contribute to the reconstitution of the normal vaginal flora and of the local physiologically acid pH. In addition to the classic formulations (cream, vaginal suppositories, and vaginal solution) for daily basis treatment, there are two innovative preparations - the gel and foam - which allow a longer persistence of the products in the application site, reaching the whole organ and including areas that are usually less accessible, such as the vaginal fornices. For these formulations, it is therefore practicable a treatment schedule limited to one application every 3 days. The primary aim of this study was to evaluate the clinical efficacy (in terms of symptoms change) and the local tolerability of the treatment with the medical device in patients affected by inflammatory-dystrophic disease in the vaginal area (vaginitis/vaginosis).

Patients and methods

Overall study design

The study was conducted according to a randomized (kind of the device used), parallel-groups, single-centered, uncontrolled design and included 75 Caucasian female outpatients randomized to receive one of the pharmaceuticals forms (cream, vaginal suppository, vaginal solution, gel, and foam; n = 15 in each group). The scheduled treatment period was maximum 12 days. The study plan included an initial visit (V1), an intermediate visit (after 6 ± 1 days of treatment) (V2) and a final visit (after 12 ± 2 days of treatment: V3). The intermediate visit could coincide with the final visit in case of recovery or almost complete resolution of symptoms. At each visit, the subjective and objective clinical state was evaluated, together with the tolerability of the device. In case of necessity, an evaluation of patients could take place at any time, even outside the scheduled visits.

Patients

Table 1 show the demographic and somatic characteristics of the patients.

Methods

Selected patients were female outpatients aged 18 - 70 years, willing to take part in the study and able to understand the study procedures and objectives documented by informed consent signature, suffering from at least two signs and of two symptoms due to a phlogistic and/or dystrophic status of the lower genital tract. Exclusion criteria were: pregnancy or breastfeeding; inadequate contraception in childbearing potential women; presence of metabolic or endocrine diseases (e.g. uncontrolled diabetes mellitus) or of other local/systemic diseases that could potentially interfere with the study parameters; concomitant treatment with antibiotics/antiseptic agents, steroidal and non-steroidal anti-inflammatory drugs, analgesics (except paracetamol as pain killer); non-therapeutic use of psychotropic substances; alcohol and/or drugs abuse; cancer; immunodepressive diseases; neurological and/or psychiatric diseases that could compromise the validity of the consent and/or the patient's adherence to study procedures; known allergy, hypersensitivity or intolerance to ingredients of study products; any medical or non-medical condition that could significantly reduce the possibility of obtaining reliable data, achieving the study objectives, completing the study; presumed poor patient's cooperation; treatment with any investigational product in the 30 days preceding the study initiation. The investigational products were locally applied every day (cream, vaginal suppositories and vaginal solution) or every 3 days (gel and foam), for 6 or (in case of persistency of significant signs/symptoms at visit 2) for 12 days. At each follow-up visit (study entry, after 6 and possibly 12 days of treatment), the presence and intensity of pain, burning, itch, dry vagina sense, dyspareunia, dysuria, vaginal discharge, and vulvovaginal erythema were checked. Signs and symptoms were quantified according to the scale: absent = 0, mild = 1, moderate = 2 and severe = 3. The overall symptoms were summarized according to the total symptoms score (TSS), defined as the sum of scores of

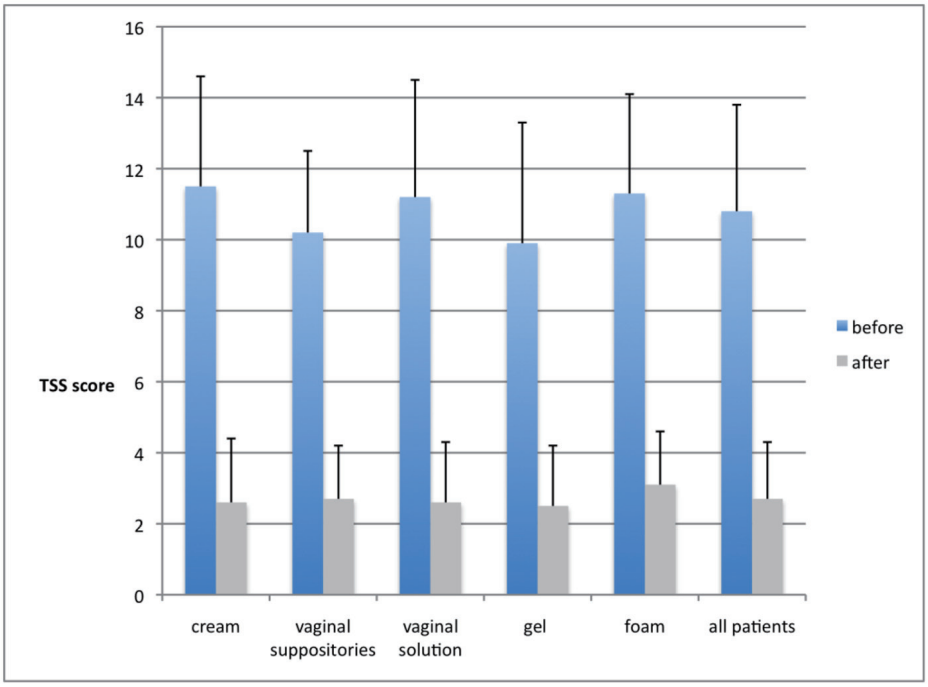

Figure 1. TSS score before and after treatment. ITT population; mean values and SD. Changes are statistically significant (P < 0.001).

all signs and symptoms. At visit 2, the percentage of responder patients, defined as a patient presenting a decrease in TSS ≥ 50% from baseline (therapeutic success), was considered as the primary efficacy endpoint. Secondary efficacy endpoints were the changes from baseline of each sign and symptom, and changes from baseline of TSS. The tolerability was evaluated on the basis of adverse events (if any).

Statistical analysis

The following populations were defined: ITT, which included all treated patients with at least one post-baseline follow-up; per-protocol (PP), which included all patients of the ITT population without major protocol violations (i.e. those violations potentially interfering with the results of efficacy and safety, such as violation of eligibility criteria, incorrect application of the devices, etc.); and safety population, which included all patients that took part in the study with evidence of at least one application of the study devices. As there were no major protocol violations, the analysis of all efficacy parameters was performed in the ITT population. The semiquantitative scores of the intensity of signs and symptoms were evaluated as frequency at any visit; mean values were calculated as well. Values of TSS at the post-baseline visits (expressed as fraction of baseline and changes from baseline) were analyzed with non-parametric tests, using the 95% confidence interval (CI) of the median values and the Wilcoxon paired test, whereas the mean values were presented as descriptive statistics. The results of therapeutic success were presented by analyzing the proportions, with their 95% CI, of responder patients (if applicable). The minimum level of statistical significance was set at a P value < 0.05 (95% CI, i.e. with alpha = 0.05). All P values and CIs were two-tailed.

Ethics and regulatory issues

The study protocol, the patient information sheet, the informed consent form, the letter to general practitioner and the "privacy statement" sheet were approved by the reference Ethic Committee of the investigational study site (Comitato Etico Campania Centro, Naples) before any study-related procedure was started. The study initiation was notified to the Italian Ministry of Health. The study was conducted according to the principles defined in the Declaration of Helsinki and in the following amendments, and to the procedures of Good Clinical Practice (whenever applicable), expressed in the guideline set out by the International Conference on Harmonization. The decision on study participation was freely taken by the patient, and it was clarified that the consent could have been withdrawn at any time, without penalty or loss of patient' rights of benefits.

Results

All patients completed the study at visit 2. The analysis of the TSS showed a statistically significant improvement of symptoms in all treatment groups (P < 0.001), with an average reduction of the initial PST similar in the different groups and ranging between 73% and 80% (with a V2/V1 ratio of 0.27 and 0.20, respectively) (Fig. 1). No clinically significant differ-

Table 2. Signs and Symptoms Mean Score Before and After Treatment

	Cream	Vaginal suppositories	Vaginal solution	Gel	Foam
Pain					
Before	1.3	0.4	0.2	0.5	0.8
After	0.6	0.1	0	0.1	0.1
Burning					
Before	1.5	1.5	1.7	1.6	1.5
After	0.3	0.5	0.5	0.5	0.3
Itch					
Before	1.3	1.2	1.7	1.3	1.2
After	0.1	0.3	0.4	0.3	0.3
Dry vagina sense					
Before	1.5	1.7	1.4	1.3	1.7
After	0.5	0.2	0.4	0.1	0.6
Dyspareunia					
Before	0.7	1.2	1.3	0.9	0.9
After	0.2	0.3	0.4	0.3	0.3
Dysuria					
Before	0.2	0.2	0.1	0.1	0.4
After	0.1	0	0	0.1	0.1
Vaginal discharge					
Before	2.4	1.9	2	1.5	1.7
After	0.5	0.8	0.5	0.5	0.5
Vulvovaginal erythema					
Before	1.7	1.3	1.7	1.6	2.0
After	0.3	0.3	0.3	0.4	0.6

ences were observed between the different preparation used. All patients achieved treatment success, defined as a PST reduction of at least 50%. No patients used rescue analgesics, not even paracetamol which was permitted by the study protocol. The intensity of individual signs and symptoms at the starting visit and the end of the study is reported in Table 2. The most common signs and symptoms at the starting visit were burning, leukorrhea and vulvo-vaginal erythema, each present in 62/75 patients (82.7). All signs and symptoms were significantly regressed or disappeared at the final visit in most of the cases; the improvement score was statistically significant ($P < 0.05$) when analyzing the total of patients, and often it resulted in a significant difference in the individual treatment groups as well, except when only a few patients had a sign/symptom at baseline. None of patients discontinued the application of the device before the schedule period. Adverse events were detected in none of the patients studied.

Discussion and Conclusions

The onset of signs and symptoms such as leukorrhea, itching, burning and pain in the vulvovaginal area is a frequent occurrence in women's life [7]. The clinical status is supported by an alteration of the physiological vaginal flora, which can be due to a proliferation of common germs (vaginosis) or to the colonization by pathogenic microorganisms (specific vaginitis) [8]. The vaginosis is the most common form and is due to the replacement of Lactobacilli normally present in the vagina (*Doderlein bacilli*, mainly represented by *L. crispatus*, *L. iners*, *L. gasseri* and *L. Jensenii*) by anaerobic germs such as *Gardenella vaginalis*, mycoplasma, etc. [9, 10]. In physiological condition, Lactobacilli produce lactic acid, hydrogen peroxide and bacitracin and they cause a local acid pH and protect vagina from infectious agents [11]. The bacteria responsible for vaginosis produce enzymes that remove the protective coating (gel layer) that covers the epithelium of the vagina and cervix [12] and at same time protein with pro-inflammatory activity. A common therapeutic approach is to use local or systemic antibiotics with reduced impact on Lactobacilli (e.g. metronidazole or clindamycin) [13]; the use of local antiseptics and probiotics [14] may be useful as well. The administration of antibiotics, however, although generally effective is not free from side effects, which make a repeated use difficult [15]. For this reason, therapeutic alternatives have been proposed, including non-steroidal anti-inflammatory drugs [16],

plant extracts [17] and agents active on the bacterial biofilm [18]. In this study, the ability of the studied medical device (cream, ovules, solution, gel, and foam) to restore the state of well-being in patients with inflammatory-dystrophic vaginal disorders was evaluated. Patients were young-adult Caucasian women (average age 39 years) with a moderate-mild symptomatic status (average admission TSS of about 11, with an actual maximum score value of 30). In all patients, there was an almost complete remission of symptoms within 6 days about of treatment, in the absence of any kind of side effects. It is interesting to note that no appreciable difference was observed in the effects of the different pharmaceutical forms used, even in the case of the gel and foam that were applied every 3 days: it is presumable that such preparations allow a longer and more widespread permanence of the product in vaginal area. Given the composition of preparations, it is reasonable to believe that the device acts contributing to the restoration of the physiological gel layer protecting the vagina (barrier effect) and probably removing the bacterial biofilms. Limitations of this study are the absence of a control group and the lack of a prospective assessment of the incidence of relapses. The identification of a control group was difficult because of the unavailability of medical devices with similar composition and indications; on the other hand, it would have been unethical to provide placebo or no treatment to the patients. Neverthless, the rate of clinical response (100%) leaves no doubt about the real effectiveness of the treatment. About the evaluation of relapses, this was not included in the aims of the investigation and it could be the topic for further clinical investigation. It must be also considered that, since there was complete absence of adverse events, the cycle of treatment might be repeated whenever considered necessary. In conclusion, the new medical device in vaginal formulations has demonstrated to be effective and safe to the local treatment of moderate-mild inflammatory-dystrophic gynecological diseases.

Author Contributions

R. Papa, M. G. Troncone and F. Altruda performed the clinical study. V. Rullo and G. Saponati wrote the study protocol, analyzed the data and revised the publication text. All authors certify that they have participated sufficiently in the intellectual content and the analysis of data. Each author has reviewed the final version of the manuscript and approved it for publication.

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