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Local Vs Systemic Antifungal Treatment of Yeast Vaginitis: Comparison of Time to Symptomatic Relief

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Abstract

Objective: Vulvovaginal candidiasis (VVC) is a common vaginal infection with bothersome symptoms including itching, burning and irritation. Since the organism causing VVC, the pharmacologic intervention recommended for treatment and the time to relief of symptoms should be considered in the management strategy for all patients, this paper revisits the ACCELERATE study. This study compared onset of symptomatic relief (the relief of vulvovaginal itching, burning or irritation) in women with vaginal yeast infections who had either used a local vaginal antifungal preparation (LVA) or systemic oral antifungal (SOA) in the context of the above factors. The date from this study can be utilized in current clinical practice, considering evolving VVC species, the high incidence of VVC, new concerns regarding pregnancy and drug interactions of oral VVC treatment and developing drug resistance to various VVC organisms.

Method: This paper presents a review of the ACCELERATE data, a study conducted in 2002. The study is a randomized, double parallel-group study of subjects diagnosed with vulvovaginal candidiasis by positive 10% KOH wet preparation, who were treated with either LVA (1200 mg miconazole nitrate ovule insert and 2% miconazole nitrate external vulvar cream) or SOA (150mg of fluconazole.) to determine first recorded time of symptom relief.

Results: In this group of subjects, the data showed that the local vaginal antifungal system provided faster median times for initial relief of the vulvovaginal candidiasis symptoms of itching, burning, and irritation individually, and for all symptoms combined, then the oral antifungal treatment.

Conclusion: VVC should be diagnosed accurately and treatment should be individualized considering the patient medical history, concomitant medications, fertility potential, time to symptom relief and personal preference. In this cohort of women, use of an LVA resulted in a four-times faster relief of symptoms than SOA, although there was no difference in overall treatment outcome.

Introduction

Vulvovaginal candidiasis (VVC) is second only to bacterial vaginosis (BV) in terms of vaginal infections seen by health care providers [1]. However, the true incidence of VVC is difficult to determine. Reasons for this difficulty include yeast not being a reportable disorder, the frequency of diagnosis by history without microscopic or laboratory confirmation, the use of over the counter (OTC) treatment without provider appointment and the natural colonization of yeast in up to 20% of women [2]. Additionally, as no OTC treatment is available for BV, presentation to a health care provider is necessary for treatment, which may falsely tilt the statistic in favor of BV.

Most VVC is secondary to Candida (C) albicans, but the non-albicans species, especially C. glabrata appear to be increasing. In symptomatic women presenting with VVC, non-albicans species range from 11-25% [3,4,5] with higher incidences in post-menopausal women, and reported increases up to 54 % in any aged woman with diabetes. [6,7]. C. glabrata is most frequently isolated, followed by C. tropicalis and C. parasiliosis [8]. Non-albicans species have been reported as high as32% in women with chronic or recurrent VVC [9].

The significance of non-albicans species lies not in symptoms, as itching, burning, and discharge are commonly seen in all species, but in the treatment options. Concerns regarding azole treatment resistance due to increased use of OTC treatment and prolonged therapy for recurrent infections have been cited in the literature [8]. Despite this, recent studies show that in the US, C. albicans has a low incidence of fluconazole resistance, approximately 0.5–2%. However, C. glabrata, and C. tropicalis and C. parapsilosis, have higher rates at 11–13%, 4–9%, and 2–6%, respectively [10]. The CDC recommends a non-fluconazole azole treatment for non-albicans infections, although the International Society for Study of Vulvovaginal Disorders (ISSVD) recommends miconazole [11,12]. For uncomplicated (VVC)many clinicians turn to aa 2007 Cochrane review, but this area of infectious disease has seen changes in medical treatment of VVC since then [13].

As clinicians often note, patient preference tends to favor oral therapy for uncomplicated VVC [14]. However, choice of therapy counseling for all women should incorporate factors which include not only their preference, but also efficacy and safety. As with any topical therapy, local, but transient skin reactions such as burning or irritation, may occur. However, oral medications carry the risk of systemic reactions, such as gastrointestinal side effects or headaches. Also of concern with oral treatment is the interaction with other medications the patient may be taking, such as statins. Health care providers should also consider the recent concerns regarding the risk of a single dose of fluconazole in early pregnancy and increased miscarriage risk [15,16]. Each patient should be looked at in context of their personal history and medical situation prior to initiation of therapy. Finally, choice of treatment should consider patient choice.

The primary objective of the ACCERLERATE study was to measure and compare the time of onset of symptomatic relief in women with vaginal yeast infection who were randomized to either a combination pack (1200 mg miconazole nitrate ovule vaginal insert and 2% miconazole nitrate external vulvar cream) or a single oral dose of 150 mg fluconazole.

Materials and Methods

Review of the ACCELERATE study, a randomized, double parallel-group study of subjects diagnosed with vulvovaginal candidiasis by positive 10% KOH wet preparation, who were treated with either LVA (1200 mg miconazole nitrate ovule insert and 2% miconazole nitrate external vulvar cream) or SOA (150mg of fluconazole.) to determine first recorded time of symptom relief.

ACCELERATE is an open-label retrospective parallel-group study with 300 subjects was conducted in 2002 to evaluate time to onset for reduction in VVC symptoms. However, with the emerging data regarding VVC, this data set was again reviewed, as the results are still applicable. Subjects were randomized to either local vaginal antifungal (LVA) or oral antifungal (OA) group. They were to record severity of symptoms baseline (immediately prior to dosing), 20 min, 40min, 1, 2, 4, 6, 12, 24, 36, 48, 60, and 72 hours after administration. Subjects were also contacted 10 days after initial therapy via telephone for a post therapy interview.

Inclusion criteria for subjects were: 1) age 18 or older; 2) non-pregnant and non-nursing; 3) positive 10% KOH slide preparation for yeast; 4) negative wet mount for trichomonas and clue cells; 5) negative Pap smear within last 12 months; and 6) total vulvovaginal sign/symptoms score of 4 or more (Figure 1).

Subjects were excluded if; 1) used antifungal or antimicrobial therapy (systemic or vaginal) within ten days of enrollment or used therapy other than study medication

during the 72-hr study period; 2) used vaginal contraceptive, medicated douche, feminine spray or other vaginal and/or vulvar product within two days of enrollment and for the duration of the study; 3) had current episode of bacterial vaginosis, Chlamydia trachomatis, Neisseria gonorrhea, HPV, trichomoniasis, herpetic lesions, condyloma or any other condition that could affect VVC response to miconazole nitrate or fluconazole; 4) history of sensitivity to imidazole or triazole class of drugs; 5) used drugs that could interact with study medications; 6) received treatment for cervical intraepithelial neoplasia or cervical carcinoma; 7) used experimental drug or device within 30 days of enrollment in study; 8) experienced more than four episodes of VVC in past 12 months, or; 9)used illicit drugs within 30 days.

Subjects randomized to the LVA were instructed to use the ovule insert at bedtime and begin application of external cream immediately, if desired. Those randomized to the OA were to ingest the tablet immediately, and the use of topical vulvar antifungals, anti-itch treatment or emollient was not allowed for study participation.

Each randomized subject was given a diary/ worksheet for either LVA or OA. Completion of the diary/ worksheet began immediately prior to study medication use. Subjects were instructed to record the time of the first application of external vulvar cream and the bedtime use of the ovule insert, or the time of ingestion of the OA. Subjects were to record self- assessment severity scores for itching, burning, and irritation at baseline/zero minutes (immediately prior to dosing), at 20 and 40 minutes, and 1, 2, 4, 6, 12, 16, 24, 36, 48, 60, and 72 hours following first administration of the external vulvar cream and/or ovule insert, or ingestion of the oral tablet. Diary entries ended each day at subject bedtime and resumed upon subject awakening.

The number and distribution of hours to symptom relief were summarized separately for itching, burning, irritation and for all symptoms combined. The time to overall symptom relief was based on the maximum time to relief of any of the symptoms of itching, burning, or irritation. (Table 2) Time-to-event analysis was applied to determine the median time to relief. Statistical significance was assessed overall using the Kaplan-Meier log-rank test. T-test was used to compare the mean of change from baseline between the two treatments.

Results

The multicenter ACCELERATE study enrolled 310 subjects. Of these 257 subjects were included in the efficacy evaluable population. Subjects were excluded for meeting one or more of the exclusion criteria, failing to meet inclusion criteria or not recording symptom score for at least two hours following medicine administration. There were 38 subjects excluded from the LVA group (n=122) and 15 subjects were excluded in the OA group (n=135). (Figure 3)

Demographic and baseline characteristics of subjects can be found in Table 2. The average age of subjects was 32.1 (STD 12.22) and 33.4 (STD 14.54). Severity of disease at admission was scored using the clinical scoring system. Mild disease is total score 2 to 6, moderate disease 7 to 12 and severe disease greater than 12. The distribution of disease severity between the LVA group and OA group is similar: mild disease 31.1% v 28.1%; moderate disease 60.6% v 61.55%; and severe disease 8.2% v 10.4%.

The median time to initial relief of itching was 1.0 hour for the 104 subjects in the LVA treatment group who reported itching at baseline. In comparison, the median time to initial relief of itching was 4.0 hours for the 123 subjects in the OA treatment group who reported itching at baseline. This is a p-value of <0.0001. (Using Kaplan-Meier values which take into consideration overall time-to-event cursors vs Wilcoxon, with its generalized comparison of treatment groups – See Table below).

The median time to initial relief of burning was 1.0 hour for the 91 subjects in the LVA treatment group who reported burning at baseline. In comparison, the median time to initial relief was 4.0 hours for the 108 subjects in the OA treatment group who reported burning at baseline. This is a p-value of 0.0894.

The median time to initial relief of irritation was 1.0 hour for the 109 subjects in the LVA treatment group who reported irritation at baseline. In comparison, the median time to initial relief was 4.0 hours for the 125 subjects in the OA treatment group who reported irritation at baseline. This is a p-value of 0.0071.

The median time to initial relief of combined symptoms was 4.0 hours for the 75 subjects in the LVA treatment group who reported itching, burning and irritation at baseline. In comparison, the median time to initial relief

CLINICAL SCORING SYSTEM Vulvovaginal Signs and Symptoms					
SYMPTOMS					**SCORE**
Itching	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Burning	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Irritation	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
SIGNS					
Edema	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Erythema	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Excoriation	Absent = 0	Mild = 1	Moderate = 2	Severe = 3	
Sum of the scores for each sign and symptom **TOTAL SCORE:**_____					

Figure 1 Scoring System Vulvovaginal Scoring System

Summary of Overall Mean Symptom Score

	Topical Miconazole				Oral Fluconazole			
Time Interval (Hours)	**Mean Symptom Score**	**Std. Dev of Mean**	**Mean Change from Baseline**	**St Dev of Mean Chance**	**Mean Symptom Score**	**Std. Dev of Mean**	**Mean Change from Baseline**	**St Dev o Mean Change**
0:00	1.50	0.94			1.70	0.92		
0:01-0:20	1.30	0.92	-0.20	0.76	1.60	0.95	-0.10	0.42
0:21-0:40	1.20	0.91	-0.30	0.85	1.50	0.91	-0.20	0.57
0:41-1:00	1.00	0.89	-0.50	0.90	1.30	0.92	-0.30	0.67
1:01-2:00	0.90	0.87	-0.60	0.93	1.20	0.89	-0.40	0.78
2:01-4:00	0.80	0.88	-0.70	0.95	1.20	0.89	-0.50	0.81
4:01-6:00	0.60	0.73	-0.80	0.92	1.10	0.89	-0.70	0.86
6:01-12:00	0.80	0.85	-0.80	1.06	0.90	0.85	-0.60	0.88
12:01-16:00	0.60	0.78	-0.90	0.99	0.80	0.87	-0.80	0.90
16:01-24:00	0.50	0.75	-1.10	1.03	0.70	0.79	-1.00	0.91
24:01-36:00	0.40	0.71	-1.20	1.07	0.50	0.75	-1.00	0.93
36:01-48:00	0.40	0.66	-1.20	1.06	0.50	0.73	-1.20	0.93
48:01-60:00	0.40	0.65	-1.20	1.05	0.40	0.66	-1.20	0.99
60:01-72:00	0.20	0.56	-1.30	1.02	0.30	0.55	-1.40	0.97
>72:00	0.30	0.56	-1.00	0.83	0.20	0.42	-0.90	0.94

Figure 2 -Note: Severity of symptoms (itching, burning and irritation) was scored as 0=absent, 1=mild, 2=moderate and 3=severe. The mean score is calculated by adding the individual non-missing score for itching, burning and irritation and then dividing by the total number of non-missing scores. T-test was used to compare the mean of change from baseline between two treatments

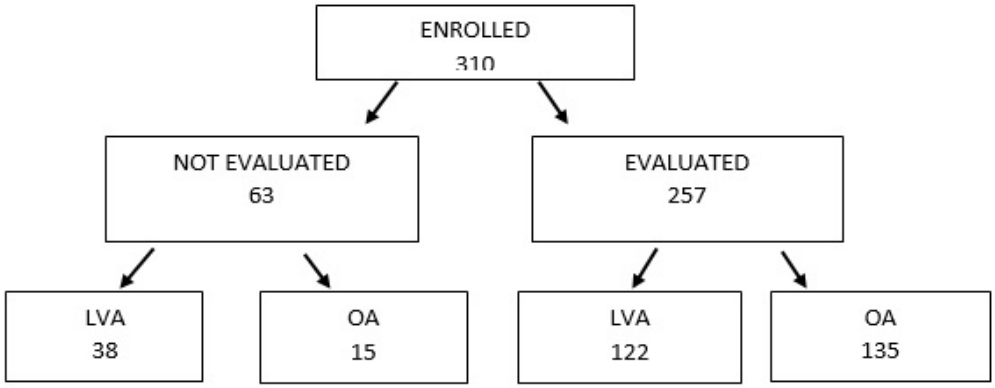

Figure 3. LVA – Local Vaginal Application; OA- Oral Administration

was 16.0 hours for the 101 subjects in the OA treatment group. Table 1 This is a p-value of 0.0010.

Although no serious adverse events were recorded in any subject10.9% of LVA and 11.4% of OA subjects reported a non-serious adverse event. The most common reaction in both groups was persistent or worsening vulvovaginal discomfort.

Discussion

VVC is common, with up to 54% of women report having experienced at least one vaginal yeast infection [17,18]. These infections are related to a higher incidence of sexual dysfunction [19]. The ACCELERATE study showed shortened time to initial relief on all VVC parameters measured, including itching, burning, irritation or a combination of all symptoms in patients randomized to LVA versus OA. There was a significant difference in reported median time to onset of relief between treatment groups, with the LVA group reporting median time to initial relief of itching, burning and irritation in1.0 hour and for all symptoms combined in 4 hours. In the OA treatment group, the median time to initial relief of symptoms was 4.0 hours, and 16.0 hours for all symptoms combined.

Conclusion

The LVA provided four-times faster median times for initial relief of the VVC symptoms of itching, burning, and irritation individually, and for all symptoms combined than the OA.

As relief of symptoms will reflect patient satisfaction, these data will assist providers in adding another parameter to their treatment recommendations.

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