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Terconazole Cream for Non-*Candida albicans* Fungal Vaginitis: Results of a Retrospective Analysis

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ABSTRACT

Objective: Although it is FDA-approved for use in vulvovaginal candidiasis caused by non-*Candida albicans* species, terconazole cream has not been been studied in patients with these infections. We sought to assess the clinical and mycological efficacy of terconazole cream in women with non-*C. albicans* vaginitis.

Methods: The records of patients who had received a 7-day course of terconazole cream for culture-proved non-*C. albicans* vaginitis were reviewed. Data with regard to patient demographics, clinical and mycologic response to therapy within 1 month of treatment, and outcome with other antifungal therapies were analyzed.

Results: Twenty-eight patients received terconazole cream for non-*C. albicans* infections. Three patients did not return for follow-up. The median age was 45 years. Seven (28%) patients were nulliparous. The median duration of symptoms was 3 years. Nine patients (36%) had received terconazole within the 6 months prior to referral. Overall, there were 20 *C. glabrata* cases, 3 *C. parapsilosis*, and 2 *C. lusitaniae*. Fourteen (56%) patients achieved a mycologic cure; 11 (44%) noted a resolution of their symptoms. Prior terconazole use was not associated with treatment failure ($P = 0.09$). Ten failures received boric acid suppositories as subsequent treatment; a cure was effected in 4 (40%). Two of three patients (67%) were eventually cured with flucytosine cream. Five (20 %) patients remained uncured.

Conclusions: Terconazole cream may be an appropriate first-line treatment for non C. albicans vaginitis, even in patients who have previously received the drug. Infect. Dis. Obstet. Gynecol. 8:240–243, 2000. © 2000 Wiley-Liss, Inc.

KEY WORDS

candidiasis; vaginitis; antifungal therapies

Fungal vaginitis is one of the most common causes of vaginitis. It is estimated that 13 million cases of vulvovaginal candidiasis (VVC) occur in the United States annually.[1,2] Although most of these infections are caused by *Candida albicans*, recent studies show that non-*C. albicans* species account for a significant proportion of cases referred to subspeciality clinics. In 1986, O'Conner and Sobel[3] found that 21% of 115 women with recurrent VVC had non-*C. albicans* species. Other centers have found 32% of VVC resulting from to non-*C. albicans* species in Philadelphia,[4] 19% in Pavia, Italy,[5] and 50% in Rome.[6] Although these studies represent diverse populations, it is clear that non-*C. albicans* are significant pathogens, regardless of geography, and concerns have been raised that infec-

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TABLE 1. Clinical and mycologic cure with different vaginal isolates

	C. glabrata (n = 20)	*C. parapsilosis* (n = 3)	*C. lusitaniae* (n = 2)	Total (n = 25)
Clinical cure (%)	8 (40)	2 (66)	1 (50)	11 (44)
Mycologic cure (%)	10 (50)	2 (66)	2 (100)	14 (56)
Negative smear (%)	12 (60)	2 (66)	2 (100)	16 (64)

tions with these pathogens are occurring more frequently.

Terconazole is approved by the Food and Drug Administration for the treatment of fungal vaginitis.[7] Advertisements for terconazole have stressed its effectiveness in non-*C. albicans* infections.[8] It has been shown to have good in vitro and in vivo effectiveness for *C. albicans*.[9,10] However, our review of the literature failed to uncover any clinical data with regard to the use of terconazole cream for non-*C. albicans* vaginitis. We report here our experience with women treated with a 7-day course of intravaginal teraconazole for non-*C. albicans* vaginitis.

MATERIALS AND METHODS

The patient population consisted of women referred by private gynecologists from 1996 through 1998 for evaluation of chronic vaginal symptoms. Each patient underwent an evaluation that included a standardized history, pelvic examination, vaginal pH determination, smears for saline and potassium hydroxide microscopy, and fungal cultures of the vulva and vagina. Fungal cultures were plated on modified Sabouraud dextrose agar plates, which were incubated for 7 days at 37°C. Positive cultures were evaluated for germ tube formation for identification of *C. albicans* species. Germ tube-negative isolates were further speciated with the Yeast-Tek System (Remel, Lenexa, KS).

In our clinic, patients who had blastospores on microscopy and no hyphae were offered a 7-day course of 0.4% intravaginal terconazole cream for presumed non-*C. albicans* infections. As part of our routine follow-up of such patients, they were asked to return immediately and 1 month after treatment to determine their clinical and mycologic response to therapy. For the present study, the records of patients with culture-proved non-*C. albicans* vaginitis were retrospectively reviewed. Patients were evaluated with regard to patient demographics, clinical resolution of symptoms (clinical cure), and status of 1 month follow-up fungal culture (mycologic cure). For those patients whose cultures were persistently positive, available data with regard to results with other therapies were analyzed. Statistical analysis was performed with the EpiInfo statistical software package v. 6.0 (Centers for Disease Control and Prevention, Atlanta, GA).

RESULTS

Twenty-eight patients were given terconazole cream for non-*C. albicans* infections. Three patients did not return for follow-up and were excluded from further analysis. The median age was 45 years (range 14–78). Seven women were nulliparous (28%). Nine (36%) were menopausal; eight of them were on some form of estrogen replacement therapy. Seven patients (28%) had findings suggestive of a nonneoplastic vulvar epithelial skin disorder. Among these patients, four had lichen sclerosus, two had squamous epithelial hyperplasia, and one had lichen planus. Fourteen patients (56%) had burning, thirteen (52%) had itching, and nine (36%) complained of dyspareunia. The mean duration of symptoms was 3 years (range 0.3–22). Nine patients (36%) had used terconazole within the last 6 months.

C. glabrata was isolated in 20 patients (80%), *C. parapsilosis* in three patients (12%), and *C. lusitaniae* in two patients (8%). Fourteen patients (56%) achieved mycologic cure with terconazole cream; among them, 11 patients (79%) noted resolution of their symptoms in conjunction with the mycological cure. Overall, 11 (44%) patients still had positive fungal cultures following terconazole therapy. Table 1 shows the rates of clinical and mycologic cure by species. Prior terconazole use was not associated with failure of treatment ($P = 0.09$). Four of ten (40%) patients with positive follow-up cultures were successfully treated with boric acid vaginal suppositories. Three patients were given flucytosine vaginal cream; two (67%) of them achieved mycologic cure. Five patients (20%) remained uncured with any of these modalities.

DISCUSSION

Because most vaginal yeast infections are caused by *C. albicans*, clinical studies of terconazole have essentially been studies of *C. albicans* infections.[11,12] In 1989, a multicenter trial evaluated the clinical effectiveness of terconazole cream in the treatment of *C. albicans* vaginitis. The clinical cure rate was 87–95%; the mycologic cure rate was 77–91%.[12] In that study, *C. albicans* was the causative organism of infection, and there were no patients with non-*C. albicans* infections. As a triazole antifungal agent, terconazole theoretically should have a relatively broad spectrum of antifungal efficacy. As a result, the drug has been extensively marketed for non-*C. albicans* vaginitis[7] and is widely accepted as first-line treatment for this type of infection. However, clinical data supporting this supposition are to our knowledge nonexistent.

In vitro, terconazole has been evaluated by Lynch and Sobel.[13] Among 100 isolates of *C. albicans*, 39 isolates of *C. glabrata*, 26 isolates of *C. parapsilosis*, and seven isolates of *C. tropicalis* tested for resistance to amphotericin B, 5-flourocytosine, ketoconazole, clotrimazole, miconazole, terconazole, itraconazole, saperconazole, and fluconazole, the authors found that non-*C. albicans* species, especially *C. glabrata*, had severalfold increases in MICs to all the azole antifungals but remained sensitive to amphotericin and 5-fluorocytosine. *C. albicans* and *C. parapsilosis* were highly sensitive to all antifungals tested. Surprisingly, terconazole had up to twofold higher MICs for *Candida* species than the other topical azoles tested. This result suggests that terconazole may actually be inferior to other azole antifungal agents for these vaginal infections. However, MICs do not seem to predict clinical susceptibility reliably and may vary extensively from one laboratory to another.[14–16] Furthermore, it is unclear whether MICs, which are essentially measures meant to mimic drug–organism interactions in blood stream infections, are applicable to the vagina, where there are greater quantities of both organism and medication. Therefore, given the concerns raised by laboratory data and the possibly increasing emergence of non-*C. albicans* infections, a review of clinical outcomes in a selected group of patients is important to guide clinical decision making.

This retrospective study demonstrates that a 7-day course of terconazole cream resulted in a mycological cure in 56% of patients with non-*C. albicans* yeast infections. However, our results are subject to certain limitations. Because our patient population is derived from a tertiary care referral center, most of these patients had been suffering from vaginal symptoms for years and had previously tried many different therapies, including multiple azole preparations. Although our data suggest that prior terconazole use was not statistically associated with current treatment failure, it is possible that terconazole cream would be even more effective in a less refractory patient population. Furthermore, in the 28% of patients with an associated nonneoplastic vulvar epithelial skin disorder, the yeast may have been more difficult to treat because of a deficiency in the local skin defenses. Finally, the retrospective nature of our study fails to account for the significant number of patients who refused to use terconazole because they had used it in the past without benefit and did not want to waste their time with another course.

Non-*C. albicans* vaginitis patients present a unique therapeutic challenge, particularly when they fail conventional therapy. In a previous study from our center, we found that, among 34 women with non-*C. albicans* vaginitis, 20 were cured with either fluconazole (2/8 patients), itraconazole (3/6), clotrimazole (4/7), or boric acid suppositories (11/13).[4] Other studies, also limited to case series, support the use of flucytosine cream, boric acid, or combination therapy in this difficult patient population. In 1985, Horowitz et al.[17] compared 18 patients with *C. tropicalis* vaginitis to 81 patients with *C. albicans* vaginitis. Patients with *C. tropicalis* had a higher rate of recurrence (33%), and their infections tended to be resistant to miconazole cream, 1% clotrimazole cream, oral ketoconazole, and 1% aqueous gentian violet lotion. None of the six patients with recurrent *C. tropicalis* vaginitis was cured by any treatment. However, in a follow-up study,[18] 15 patients with *C. tropicalis* infections responded to flucytosine, although the length of follow-up is not clear. Sobel and Chaim[19] reviewed the charts of 80 women with *C. glabrata* infections who had been treated with boric acid suppositories. They found that boric acid resulted in a mycologic cure in 50% of patients. Finally, White and colleagues[20] looked at three cases of *C. glabrata* vaginitis that were clinically resistant to fluconazole,

itraconazole, or nystatin pessaries; two responded to prolonged treatment with itraconazole in conjuction with nystatin pessaries.

The paucity of clinical data with regard to non-*C. albicans* vaginitis underscores the need for prospective studies to address the best methods for treatment. However, the feasibility of such studies is severely limited, insofar as these infections are often identified at referral centers, which may select for a more difficult patient population, and because there is currently no surveillance of these infections in other women. Nevertheless, our results suggest that terconazole has at least some role to play in management of these women and may be comparable to other potential treatment modalities.

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