A randomized clinical trial of the efficacy and safety of terconazole vaginal suppository versus oral fluconazole for treating severe vulvovaginal candidiasis

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Abstract

Terconazole is a new, broad-spectrum, triazole antifungal agent. The aim of this study was to compare the efficacy and safety of a 6-day course of a terconazole vaginal suppository (80 mg) with two doses of oral fluconazole (150 mg) for the treatment of severe vulvovaginal candidiasis (SVVC). In this prospective, randomized case-control study, 140 consecutive patients with SVVC were enrolled at the Department of Obstetrics and Gynecology of Peking University Shenzhen Hospital from July 1, 2013, through June 31, 2014. Patients with SVVC, initially at a 1:1 ratio, were randomly assigned to receive treatment with either the terconazole vaginal suppository or oral fluconazole. The patients had follow-up visits at 7–14 days and 30–35 days following the last dose of therapy. The clinical cure rates in the terconazole group and the fluconazole group were, respectively, 81.0% (47/58) and 75.8% (50/66) at follow-up day 7–14 and 60.3% (35/58) and 56.1% (37/66) at day 30–35. The mycological cure rates in the two groups were, respectively, 79.3% (46/58) and 71.2% (47/66) at follow-up day 7–14 and 62.1% (36/58) and 53.0% (35/66) at day 30–35 (P > .05 for all). Local irritation was the primary adverse event associated with terconazole, whereas systemic side effects were associated with fluconazole; however, these effects were minimal. This study demonstrated that a terconazole vaginal suppository (80 mg daily for 6 days) was as effective as two dose of oral fluconazole (150 mg) in the treatment of patients with SVVC; as such, terconazole could be a choice for therapy of this disorder.

Key words: vulvovaginal candidiasis, terconazole, fluconazole.
Introduction

Vulvovaginal candidiasis (VVC), which affects up to 75% of women of child-bearing age at least once in their lifetime, is predominantly caused by Candida albicans [1–5]. Sobel et al. [6] classified VVC into complicated VVC and uncomplicated VVC. In its Sexually Transmitted Diseases Treatment Guidelines, the CDC recommends VVC treatment on the basis of its classification [7]. Women with severe VVC (SVVC) might not adequately respond to single-dose treatment [3,7], and the CDC recommends two doses of 150 mg of oral fluconazole for the treatment of these women [7]. Terconazole is a new triazole ketal derivative with potent and broad-spectrum antifungal activities. Studies from Europe and the United States have demonstrated the efficacy of a terconazole vaginal suppository in the treatment of uncomplicated VVC [8–17]. Several clinical guidelines recommend the use of terconazole for the treatment of VVC [7,18–20]. However, these recommendations have not been validated using prospective studies. Accordingly, we performed a prospective, randomized study in patients with SVVC to determine whether an 80-mg daily terconazole vaginal suppository for 6 days was as effective as two doses of 150 mg of oral fluconazole.

Materials and methods

Study design

This clinical trial was an open, randomized, parallel design study conducted at the Gynecological Clinic, Peking University Shenzhen Hospital, from July 1, 2013, through June 31, 2014 (Clinical Trials Identifier: NCT02180100). Prior to the initiation of the study, the protocol and informed consent form were reviewed and approved by the hospital review board. After informed consent was obtained, patients with SVVC were equally randomized to receive either an 80-mg vaginal terconazole suppository inserted daily for six consecutive days (terconazole group) or two doses of 150 mg of oral fluconazole (fluconazole group).

Case definition

VVC was defined as the presence of symptoms, the demonstration of blastospores and pseudohyphae in a wet vaginal smear treated with 10% potassium hydroxide, and a positive fungal culture. All strains were identified using the API Candida system (bioMerieux, Marcy l’Etoile, France).

VVC classification

The severity of each symptom and sign, such as itching, burning, discharge, and erythema, was assigned a score based on the following scale: 0 = absent; 1 = mild; 2 = moderate; and 3 = severe. Patients with a severity score of 7 or greater were designated as having SVVC. Uncomplicated VVC was defined as mild-to-moderate sporadic VVC caused by strains of Candida albicans in normal, non-pregnant women. Recurrent VVC was defined as four or more episodes of VVC that occurred during the previous 12-month period [7].

Vaginal samples

A sample from the lateral vagina wall was obtained with a sterile cotton-tipped swab. The swab was placed in a tube filled with saline for direct microscopic examination with 10% potassium hydroxide. Culture was simultaneously performed for all cases of positive wet vaginal smear.

Identification methods

Specimens were plated on CHROMagar (Biocell Laboratory Ltd., Zhengzhou, China) for 24 to 48 hours at 37°C in ambient air. Strains were identified using the standardised system API Candida and stored in medium containing 2% glucose, 2% peptone and 20% glycerol at −70°C.

Antifungal susceptibility testing

The in vitro antifungal susceptibility of the Candida strains from the patients was tested using a broth microdilution method according to the CLSI M27-A3 guidelines, utilising a pH of 7. The susceptibility results were analyzed using the same criteria for fluconazole (S: ≤8 μg/ml; SDD: 16–32 μg/ml, and R: ≥64 μg/ml) [21]. Quality control isolates from the American Type Culture Collection (ATCC90028) were assayed under the same conditions.

Admission criteria

The patients who were admitted to the trial were generally healthy, 18–50 year-old women with SVVC. Patients with uncomplicated VVC and recurrent VVC were excluded from the study. Enrolled patients agreed to abstain from sexual intercourse during the treatment period or use condoms for the remainder of the study period. During the study, they also agreed to abstain from using any other vaginal product. Patients were excluded from the study if they: (1) had any other sexually transmitted disease or gynecological abnormality requiring treatment; (2) had a disease known to predispose to candidiasis, such as diabetes mellitus, or were receiving antibiotics or corticosteroids; (3) were pregnant; (4) had used antifungal medication in the week before entry; (5) were expected to menstruate within
seven days of the start of treatment; or (6) were infected with more than one Candida species.

Treatment regimens

Patients who met the study entry criteria were randomized at a 1:1 ratio at the first visit to receive either an 80-mg terconazole vaginal suppository that inserted intravaginally daily for 6 days (Shanghai Shyndec Pharmaceutical CO., LTD, Shanghai) or 150 mg of oral fluconazole (Pfizer Pharmaceuticals Ltd, Dalian) on days 1 and 4. Sexual abstinence was advised until after the 30–35 day follow-up.

Follow-up visits

Patients were required to return to the Gynecological Clinic for a follow-up visit 14 (7–14) days and 35 (30–35) days following the last dose of therapy. During these visits, the patient was questioned about any adverse events or concomitant medications. Signs and symptoms were scored, recorded, and compared with the baseline severity assessment using the same scoring system. Clinically, a cure was defined as the resolution of signs and symptoms present at baseline, with a total severity score of ≤2. Improvement was defined as a considerable reduction in the severity of baseline signs and symptoms, with a decrease in total score of ≥50%. Patients who were not clinically cured or improved were considered clinical failures [22]. Mycological cure or failure was defined as Candida negative or positive by cultures obtained during the follow-up visits (Fig. 1).

Statistical methods

This study was primarily designed to determine whether terconazole vaginal suppositories were as effective as oral fluconazole capsules for the treatment of SVVC. We calculated the sample size using a method that takes into account the intracluster correlation coefficient, the number of events, the expected effect and the power of the study. Assuming that fluconazole therapy would have a clinical success rate of 80%, an estimated 132 patients (allowing for a drop-out rate of 30%) would be required in each treatment group to detect a treatment difference of 10%, with 80% power and a two-sided alpha level of 0.05.

Therapy outcomes were analyzed using a chi-square test to compare the results of treatment at the short- and long-term visits. Student t-test was used to compare the difference between the mean ages of the patients. Statistical significance was set at $P < .05$. Statistical analysis of the data was performed using SPSS 10.0 (SPSS Inc., Chicago, IL).

Results

Patients and Candida strains

A total of 140 patients were enrolled and finished the study. The patients were 29.81 (19–45) and 29.81 (19–45) years old in the terconazole group and fluconazole group, respectively. Most (92.9%, 130/140) cases were caused by C. albicans. Non-albicans Candida included C. glabrata (5%, 7/140), C. parapsilosis (1.4%, 2/140), and C. tropicalis (0.7%, 1/140). In sum, 30 of the 140 patients had a history of antibiotic therapy prior to the development of VVC. The demographic characteristics and Candida species of the patients are shown in Table 1.

Efficacy

Efficacy analyses were performed on both the intention to treat (ITT) and per-protocol set (PPS). However, because the results in the ITT group were similar to those of the PPS, only results based on PPS are presented. The clinical cure rates of the terconazole group and the fluconazole group were, respectively, 81.0% (47/58) and 75.8% (50/66) at follow-up day 7–14 and 60.3% (35/58) and 56.1% (37/66) at day 30–35. The mycological cure rates of the two groups were, respectively, 79.3% (46/58) and 71.2% (47/66) at follow-up day 7–14 and 62.1% (36/58) and 53.0% (35/66) at day 30–35 ($P > .05$ for all; Table 2).

Overall, seven cases of VVC were caused by C. glabrata, of which five were treated with fluconazole and two were treated with terconazole. Three patients were positive for Candida at follow-up (all in the fluconazole group). One case of VVC caused by C. parapsilosis and one case of VVC caused by C. tropicalis were treated with fluconazole, whereas one case of VVC caused by C. parapsilosis was treated with terconazole. Only one case of VVC caused by C. parapsilosis was cured with terconazole.

Antifungal susceptibility

Antifungal susceptibility testing was conducted in 140 Candida strains isolated from patients with SVVC. The MIC90 of terconazole and fluconazole for C. albicans were 8 and 4 μg/ml, respectively ($P < .05$). The MIC90 of terconazole for C. glabrata was lower than that of fluconazole (32 vs. 8 μg/ml, respectively) ($P < .05$). The MIC90s for terconazole when used for the treatment of C. parapsilosis and C. tropicalis were lower than those for fluconazole. The MICs for terconazole against C. albicans in the mycological failure and cure groups were 1.23 μg/ml and 0.72 μg/ml, respectively ($F = 0.001, P > .05$). Of the 130 C. albicans isolates, none were fluconazole-resistant. The in vitro susceptibilities of 140 yeast isolates to terconazole and fluconazole
Assessed for eligibility (n=181)
- Excluded (n=41)
  - Declined to participate (n=26)
  - Pregnant (n=5)
  - No sexual intercourse history (n=2)
  - Near menstruation (n=3)
  - Mixed infections (n=3)
  - Other reasons (n=2)

Randomised (n=140)

Allocated to intervention (n=70)
- Received allocated intervention (n=66)
- Did not receive allocated intervention (n=4, withdraw)

Lost to first follow-up (n=3)
Lost to second follow-up (n=5)

Analysed (n=58)
- Excluded from analysis (n=12, withdraw 4, drop out 8)

Allocated to intervention (n=70)
- Received allocated intervention (n=70)
- Did not receive allocated intervention (n=0)

Lost to first follow-up (n=1)
Lost to second follow-up (n=3)

Analysed (n=66)
- Excluded from analysis (n=4, drop out)

**Figure 1.** Flow diagram of patients through trial.

Based on the National Committee for Clinical Laboratory Standards (NCCLS) M27-A3 broth microdilution method are shown in Table 3.

**Safety**

Both the terconazole vaginal suppository and oral fluconazole treatments were extremely well-tolerated. No patients discontinued the study because of severe adverse reactions. Local irritation was the primary adverse event of terconazole (Table 4).

**Discussion**

Therapeutic efficacy of treatment for SVVC

Sobel et al. [22] studied 398 patients with complicated VVC, of whom 197 were randomized to single-dose fluconazole and 201 received two sequential doses of fluconazole. They found that women with SVVC achieve superior clinical and mycological eradication with a two-dose fluconazole regimen. Currently, the two-dose oral fluconazole regimen is the standard regimen for the treatment of complicated VVC, particularly SVVC [7].
### Table 1. Characteristics and Candida species of patients with severe vulvovaginal candidiasis in the terconazole group and fluconazole group (PPS).

<table>
<thead>
<tr>
<th>Characteristics and Candida species</th>
<th>Terconazole group (n,%)</th>
<th>Fluconazole group (n,%)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ages</td>
<td>31</td>
<td>29.6</td>
<td>−3.80–0.99</td>
<td>0.2490</td>
</tr>
<tr>
<td>VCC scores at baseline</td>
<td>7.9±0.14</td>
<td>8.0±0.13</td>
<td>−0.31–0.43</td>
<td>0.7348</td>
</tr>
<tr>
<td><strong>Candida species</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. albicans</em></td>
<td>67 (95.7)</td>
<td>63 (90.0)</td>
<td></td>
<td>0.671</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>2 (2.9)</td>
<td>5 (7.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>1 (1.4)</td>
<td>1 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>0 (0)</td>
<td>1 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>70</td>
<td>70</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Note: CI, confidence interval; OR, odds ratio.

### Table 2. Comparison of the therapeutic efficacy of terconazole and fluconazole (PPS).

<table>
<thead>
<tr>
<th>Therapeutic efficacy</th>
<th>Terconazole group (n,%)</th>
<th>Fluconazole group (n,%)</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Day 7–14</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>58</td>
<td>66</td>
<td></td>
<td>0.776</td>
</tr>
<tr>
<td>Cure</td>
<td>47 (81.0)</td>
<td>50 (75.8)</td>
<td>1.367 (0.576, 3.247)</td>
<td>0.477</td>
</tr>
<tr>
<td>Improvement</td>
<td>7 (12.1)</td>
<td>10 (15.2)</td>
<td>0.769 (0.272, 2.170)</td>
<td>0.619</td>
</tr>
<tr>
<td>Failure</td>
<td>4 (6.9)</td>
<td>6 (9.1)</td>
<td>0.741 (0.198, 2.766)</td>
<td>0.749</td>
</tr>
<tr>
<td>Mycological cure</td>
<td>46 (79.3)</td>
<td>47 (71.2)</td>
<td>0.645 (0.282, 1.479)</td>
<td>0.299</td>
</tr>
<tr>
<td><strong>Day 28–35</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clinical</td>
<td>58</td>
<td>66</td>
<td></td>
<td>0.819</td>
</tr>
<tr>
<td>Cure</td>
<td>35 (60.3)</td>
<td>37 (56.1)</td>
<td>1.193 (0.583, 2.441)</td>
<td>0.630</td>
</tr>
<tr>
<td>Improvement</td>
<td>5 (8.6)</td>
<td>5 (7.6)</td>
<td>1.151 (0.316, 4.194)</td>
<td>1.000</td>
</tr>
<tr>
<td>Failure</td>
<td>18 (31.0)</td>
<td>24 (36.4)</td>
<td>0.788 (0.372, 1.665)</td>
<td>0.532</td>
</tr>
<tr>
<td>Mycological cure</td>
<td>36 (62.1)</td>
<td>35 (53.0)</td>
<td>1.449 (0.707, 2.971)</td>
<td>0.310</td>
</tr>
</tbody>
</table>

Note: CI, confidence interval; OR, odds ratio.

### Table 3. In vitro susceptibilities of 140 yeast isolates to terconazole and fluconazole according to the NCCLS M27-A broth microdilution method.

<table>
<thead>
<tr>
<th>Yeast species</th>
<th>MIC (μg/ml)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Fluconazole</td>
<td>Terconazole</td>
</tr>
<tr>
<td></td>
<td>Range</td>
<td>Geometric mean</td>
</tr>
<tr>
<td><em>C. albicans</em> (n = 130)</td>
<td>0.125, 16</td>
<td>0.63</td>
</tr>
<tr>
<td><em>C. glabrata</em> (n = 7)</td>
<td>1, 32</td>
<td>9.75</td>
</tr>
<tr>
<td><em>C. parapsilosis</em> (n = 2)</td>
<td>0.25</td>
<td>0.25</td>
</tr>
<tr>
<td><em>C. tropicalis</em> (n = 1)</td>
<td>16</td>
<td>16</td>
</tr>
</tbody>
</table>

Note: MIC, minimum inhibitory concentration.

Terconazole is a new broad-spectrum antifungal agent for the treatment of VVC. The basic mechanism of action of terconazole, which inhibits fungal cytochrome P-450, is similar to that of imidazoles [23,24]. Clinical studies of the terconazole vaginal suppository have demonstrated its efficacy in the treatment of VVC [9,16,17,25,26].

For SVVC, the present study demonstrated that the clinical and mycological cure rates after daily treatment with an 80-mg terconazole vaginal suppository for 6 days were equivalent to two doses of oral fluconazole using a 150 mg regimen.

*C. albicans* is the predominant Candida species in VVC (92.9%) and RVVC patients (93.9%) [27]. VVC caused by *C. glabrata* is associated with a lower cure rate (35%) and a higher rate of azole resistance [2,28,29] than VVC caused by other Candida spp. VVC caused by *C. glabrata*
is associated with a higher mycological cure rate when treated with a boric acid regimen, 600 mg daily for 2–3 weeks, or intravaginal fluconosine cream for 14 days [28,30]. Gomez-Moyano et al. reported two cases of VVC caused by fluconazole-resistant *C. glabrata* that were successfully treated with voriconazole, 400 mg/12 h on the first day and subsequently 200 mg every 12 h for 14 days [31]. In the current study, terconazole cured the two cases of VVC caused by *C. glabrata* and one case of VVC caused by *C. parapsilosis*, which suggests that terconazole should be a first choice for treating these infections.

**In vitro antifungal susceptibility**

Terconazole has broad-spectrum antifungal activity in vitro [32–36]. The minimum inhibitory concentrations of *C. albicans*, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* for terconazole are significantly lower than those for fluconazole [29].

No NCCLS MIC cutoff values for the *in vitro* susceptibility of terconazole are currently available. In this study, we compared the MICs for terconazole with those for fluconazole against clinical isolates of *Candida* spp. The MICs for terconazole were lower than those for fluconazole against *C. albicans* and *C. glabrata*, which suggests that terconazole is more active than fluconazole against *Candida* spp. The geometric mean of the MIC for terconazole against *C. albicans* was lower in the mycological cure group than that in the mycological failure group; however, this difference was not statistically significant. This finding supports the need for *in vitro* susceptibility testing for terconazole.

**Safety**

Studies have demonstrated the safety of the terconazole vaginal suppository; no life-threatening side effects occurred with either of the regimens. The frequency of common side effects in this study was similar to other topical antifungal agents, such as miconazole nitrate formulations [9,25]. Anaphylaxis and toxic epidermal necrolysis have been reported during terconazole therapy [37]. The genotoxicity data for terconazole have been uniformly negative. The drug is non-mutagenic in bacterial assays, and no significant effects were observed in an in vivo mouse micronucleus test and a dominant lethal assay [38]. In the present study, the adverse drug reaction of terconazole was primarily local, and no patient discontinued her treatment because of severe adverse reactions.

The current study indicates that the clinical and mycological cure rates after treatment with a daily 80-mg terconazole vaginal suppository for 6 days is equivalent to two doses of oral fluconazole using a 150 mg regimen for the treatment of patients with SVVC. Thus, the terconazole vaginal suppository is a safe and effective alternative for the treatment of SVVC.

**Acknowledgments**

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**Declaration of interest**

The authors report no conflicts of interest. The authors alone are responsible for the content and the writing of the paper.

**References**


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**Table 4. Comparison of the adverse events in the terconazole group and fluconazole group (ITT).**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Terconazole group</th>
<th>Fluconazole group</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vulvovaginal pruritus, burning and irritation</td>
<td>23 (n,%)</td>
<td>0 (n,%)</td>
<td>-</td>
<td>X² = 30.51, P &lt; .01</td>
</tr>
<tr>
<td>Systemic: fever, tachycardia, etc.</td>
<td>6 (n,%)</td>
<td>3 (n,%)</td>
<td>2.316 (0.554, 9.682)</td>
<td>P = .309*</td>
</tr>
<tr>
<td>Gastrointestinal tract: abdominal pain, diarrhea, etc.</td>
<td>3 (n,%)</td>
<td>4 (n,%)</td>
<td>0.813 (0.173, 3.781)</td>
<td>P = 1.000*</td>
</tr>
<tr>
<td>Nervous system: dizziness, fatigue, etc.</td>
<td>3 (n,%)</td>
<td>8 (n,%)</td>
<td>0.381 (0.096, 1.506)</td>
<td>X² = 2.01, P = .156*</td>
</tr>
<tr>
<td>Skin- sensitivity, etc.</td>
<td>0 (n,%)</td>
<td>3 (n,%)</td>
<td>-</td>
<td>P = .246*</td>
</tr>
</tbody>
</table>

Note: CI, confidence interval; OR, odds ratio.
*Fisher’s X².*