A Randomized Study of the Use of Fluconazole in Continuous versus Episodic Therapy in Patients with Advanced HIV Infection and a History of Oropharyngeal Candidiasis: AIDS Clinical Trials Group Study 323/Mycoses Study Group Study 40

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(See the editorial commentary by Bozzette on pages 1481–2)

Background. In human immunodeficiency virus (HIV)–infected patients, fluconazole prophylaxis is associated with reductions in the rate of fungal infection. However, concerns exist with regard to the use of fluconazole prophylaxis and the risk of development of fluconazole treatment–refractory infections.

Methods. We performed a randomized, open-label trial that compared oral fluconazole given continuously (200 mg 3 times weekly; the “continuous fluconazole arm”) with fluconazole that was provided only for episodes of oropharyngeal candidiasis (OPC) or esophageal candidiasis (EC) (the “episodic fluconazole arm”) in HIV-infected persons with CD4+ T cell counts of <150 cells/mm3 and a history of OPC. The primary study end point was the time to development of fluconazole-refractory OPC or EC, which was defined as lack of response to 200 mg fluconazole given daily for 14 or 21 days, respectively.

Results. A total of 413 subjects were randomized to receive continuous fluconazole, and 416 were randomized to receive episodic fluconazole. After 42 months, 17 subjects (4.1%) in the continuous fluconazole arm developed fluconazole-refractory OPC or EC infections, compared with 18 subjects (4.3%) in the episodic fluconazole arm, with no difference between treatment arms with regard to the time to development of a fluconazole-refractory infection within 24 months (P = .88, by log-rank test) or before the end of the study (P = .97, by the log-rank test). Continuous fluconazole therapy was associated with fewer cases of OPC or EC (0.29 vs. 1.08 episodes per patient-year; P < .0001) and fewer invasive fungal infections (15 vs. 28 episodes; P = .04, by χ2 test), but not with improved survival, compared with episodic fluconazole therapy.

Conclusion. Continuous fluconazole therapy is not associated with significant risk of fluconazole-refractory OPC or EC, compared with episodic fluconazole therapy, in HIV-infected patients with access to active antiretroviral therapy.

Oropharyngeal candidiasis (OPC) is the most common opportunistic infection among HIV-infected individuals [1, 2]. Although the incidence of OPC has decreased among persons with access to HAART [3–5], OPC and invasive fungal infections continue to occur frequently in HIV-infected persons who live in resource-limited settings [6–9]. Once fluconazole use became common for treatment and prevention of OPC, reports of mucosal candidiasis that was unresponsive to fluconazole followed [10–16]. Candida albicans is the organism most commonly isolated from patients with fluconazole-refractory OPC. These organisms frequently demonstrate reduced in vitro susceptibility to fluconazole [17], and cross-resistance to other azole agents often limits therapeutic options.
Attempts to define risks for fluconazole-refractory OPC have identified low CD4+ T cell count and fluconazole exposure as risk factors [18, 19]. A limitation of earlier studies was that fluconazole use was largely uncontrolled. Furthermore, these studies were performed before the availability of HAART. Despite the frequent use of fluconazole by HIV-infected persons, it remains unknown whether continuous fluconazole use results in a greater incidence of fluconazole-refractory disease than does fluconazole used only to treat of episodes of candidiasis. This study was designed to compare the effects of continuous fluconazole therapy with the effects of fluconazole used only for documented infections on the development of fluconazole-refractory mucosal Candida infections (FRIs).

METHODS

This study was a prospective, randomized, multiple-center, open-label trial that compared 2 different long-term fluconazole management strategies for HIV-infected persons with CD4+ T cell counts of ≤150 cells/mm³ and a history of OPC. The primary end point was the time to development of an FRI. Secondary objectives included comparisons of the 2 strategies with respect to incident mucosal infections, invasive fungal infections, nonfungal opportunistic infections, and mortality.

Study Participants

The human experimentation guidelines of the US Department of Health and Human Services and of the investigators' institutions were followed. Entry required informed consent, documentation of HIV infection, and a CD4+ T cell count of ≤150 cells/mm³ and a history of OPC. Persons aged ≥13 years and who weighed ≥40 kg were eligible. Women of childbearing potential were required to have a negative pregnancy test result and to agree to use birth control or practice abstinence. The initial entry criteria required subjects to have experienced at least 1 documented OPC episode within the 6 months before randomization.

Subjects with OPC present at screening were offered 400 mg of oral fluconazole (day 1), followed by 200 mg of fluconazole daily for an additional 6–13 days via step 1 of the protocol. Subjects who responded to step 1 therapy were offered enrollment into the long-term portion of the study (step 2). Subjects without OPC present at screening were randomized directly into step 2.

Exclusion criteria included the following: prior FRI,azole allergy or intolerance, development of ≥3 episodes of OPC within 12 weeks before study entry, history of EC, need for systemic antifungal therapy, receipt of >1 month of continuous systemic or oral topical antifungal therapy within the past 3 months, severe liver disease, serum creatinine level of ≥3.0 times the upper limit of normal, or hemoglobin concentration of <8.0 g/dL. Subjects who initiated treatment for opportunistic infections within the 14 days before study entry were ineligible, as were subjects who received medication(s) for which coadministration with fluconazole is contraindicated. Eligibility criteria were modified after 17 months to improve subject accrual. The modifications allowed individuals who experienced OPC within 24 months or an episode of EC ≥6 months before screening to enroll.

Study Design

Long-term treatment strategy assignments. Eligible subjects were randomized at a ratio of 1:1 to undergo 1 of 2 different management strategies. In the continuous fluconazole strategy, subjects received 200 mg of fluconazole orally 3 times weekly on a continuous basis. In the episodic fluconazole strategy, fluconazole was administered only for OPC or EC episodes.

Evaluations, treatment of OPC and EC, and end point determinations. Subjects were scheduled for visits every 8 weeks for examinations and between scheduled visits if signs or symptoms of candidiasis developed. At visits, subjects with signs or symptoms of OPC had swab specimens obtained from the oral mucosa to visualize Candida species by potassium hydroxide, Gram, or calcofluor white staining. At selected study centers, samples were also obtained for culture. An episode of OPC was confirmed if organisms consistent with Candida species were visualized. An episode was classified as probable if (1) staining either did not reveal Candida species or was not performed, and (2) the investigator believed that mucosal infection was present. Subjects were classified as having confirmed EC if there was cytolologic evidence of Candida organisms in specimens from the esophagus. A diagnosis of probable EC was made for patients with confirmed OPC accompanied by esophageal symptoms.

Regardless of study arm assignment, all episodes of OPC were treated with a single dose of oral fluconazole (400 mg) given on the first day, followed by 200 mg daily for 6 days. After completion of 7 days of fluconazole therapy, subjects who responded completely resumed treatment in accordance with their originally assigned long-term strategy. Subjects without improvement met the criteria for an FRI end point and discontinued study treatment. Subjects for whom OPC remained but improved after 7 days received fluconazole (200 mg daily) for an additional 7 days. Subjects who were provided 14 days of fluconazole were examined after completion of therapy. Those with persistent OPC were considered to have an FRI and discontinued study treatment. Those who responded completely resumed treatment in accordance with their assigned strategy.

Treatment for EC included a single oral or intravenous dose of fluconazole (400 mg) on the first day, followed by 200 mg of fluconazole daily for an additional 20 days. A subject was considered to have an FRI if (1) signs or symptoms of EC
worsened after 7 days of therapy and either endoscopically confirmed EC or worsening OPC occurred, accompanied by esophageal symptoms; (2) OPC remained after 14 days of therapy for EC; or (3) OPC or confirmed EC was present after 21 days of therapy. All subjects with FRIs discontinued the study treatment regimen. Subjects who were successfully treated for EC resumed treatment in accordance with their assigned strategy.

Subjects assigned to episodic fluconazole were allowed to receive continuous fluconazole (after protocol chair approval) if they experienced frequent episodes of OPC, which was defined as $\geq 3$ episodes of successfully treated OPC during a 12-week period, or a single episode of successfully treated EC. Likewise, subjects receiving continuous fluconazole at 200 mg 3 times weekly could receive continuous fluconazole at 200 mg daily if frequent episodes of OPC or EC occurred. Any subject who received continuous fluconazole at 200 mg daily who experienced a single episode of OPC or EC met the FRI end point.

**Culture and susceptibility testing.** Oral samples were obtained for fungal culture from all subjects at study entry and completion, regardless of whether infection was present. Oral cultures were performed for all patients with FRIs. At selected study sites, culture samples were obtained for each OPC episode, and esophageal culture samples were obtained at the time of endoscopy. Samples were obtained using a cotton-tipped swab and were inoculated onto Sabouraud dextrose agar slants containing chloramphenicol. Slants were shipped to a central laboratory and were subcultured onto CHROMagar *Candida* plates (Hardy Diagnostics). The species of the isolates was determined by standard procedures, and susceptibility to fluconazole was measured using the M27-A procedure [20].

**Other laboratory testing.** Hematological tests and determination of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, total bilirubin, and lactate dehydrogenase levels and CD4+ T cell counts were performed at baseline and every 24 weeks thereafter.

**Statistical Considerations**

**Sample size.** The primary study objective was to compare the impact of fluconazole used in different strategies (episodic or continuous) on the time to development of FRI. We hypothesized that after 24 months, 7% of continuous therapy recipients would develop FRI, whereas no more than 2.5% of episodic therapy recipients would develop FRI. Because it was anticipated that 10% of subjects assigned to the episodic fluconazole arm would be switched to the continuous fluconazole arm, it was estimated that 2.95% of subjects randomized to the episodic arm would develop FRI. The sample size was based on the log-rank test to determine the equality of the distributions for failure of suppression of FRI for the 2 strategies. On the basis of these assumptions and of the estimated rate of loss to follow-up of 35%, a sample size of 948 subjects (474 subjects per arm) was required. We designed the study to demonstrate superiority of one of these strategies with 80% power, a 2-sided type I error of 0.05, 12-month accrual, and 24-month follow-up duration after the last subject was enrolled. Because accrual was slow, the study remained open to accrual 24 months longer than planned. Also, fewer “cross-over events” occurred than were expected. Therefore, the study had a post hoc power of 72% to detect a 2.7% difference in FRIs between treatment strategies.

**Statistical analysis.** $\chi^2$ Analyses were used to compare baseline categorical variables, and the Kruskal-Wallis test was used for nominal variables. The primary end point was time to development of an FRI over a 24-month period. For each strategy, a Kaplan-Meier curve was constructed, and the curves were compared using the log-rank test.

**RESULTS**

During the period from May 1997 through April 2000, a total of 829 subjects enrolled in the study; 416 were randomized to the episodic fluconazole arm, and 413 were randomized to the continuous fluconazole arm. The study closed to accrual on 30 April 2000, and follow-up was completed 6 months later.

**Baseline characteristics.** Baseline characteristics of randomized subjects are shown in table 1. In the 6 months before study entry, 811 (98%) of 829 subjects experienced at least 1 episode of OPC. A total of 408 subjects had OPC present at screening, and 314 of these 408 subjects were successfully treated with fluconazole (step 1) and entered the long-term randomized portion (step 2) of the study. The reasons for excluding step 1–treated subjects from the study are summarized in figure 1. The remaining 515 subjects enrolled directly into step 2.

At baseline, 82% of participants were receiving antiretroviral therapy. There were no significant differences between study arms with regard to the use of specific classes of antiretrovirals. Antibiotic use (most often use of trimethoprim-sulfamethoxazole for prophylaxis) was reported in 81% of subjects.

**Study follow-up.** A total of 440 (53%) of the 829 participants who entered step 2 of the study completed the treatment strategy portion of the study. Reasons for discontinuation of subjects from step 2 are summarized in figure 1. Subjects who discontinued step 2 were still observed with regard to survival. A total of 464 subjects remained in survival follow-up at study completion. The median duration of follow-up for all subjects was 24 months (range, <1 to 44 months). In total, the study included 1273 patient-years of follow-up. There were no significant differences in the proportion of early terminations or follow-up durations between treatment arms. Thirty-five subjects randomized to the episodic fluconazole arm were later
Table 1. Baseline characteristics of participants in a study of continuous versus episodic fluconazole therapy.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fluconazole regimen</th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
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<tbody>
<tr>
<td></td>
<td>All</td>
<td>Episodic therapy</td>
<td>Continuous therapy</td>
<td>P (^a)</td>
<td></td>
</tr>
<tr>
<td>Randomization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>829 (100)</td>
<td>416 (50)</td>
<td>413 (50)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Following step 1 treatment</td>
<td>314 (38)</td>
<td>159 (38)</td>
<td>155 (38)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Entered directly into study</td>
<td>515 (62)</td>
<td>257 (62)</td>
<td>258 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, median years (range)</td>
<td>38 (19–71)</td>
<td>38 (19–67)</td>
<td>38 (21–71)</td>
<td>.31</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>680 (82)</td>
<td>346 (83)</td>
<td>334 (81)</td>
<td>.42</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>149 (18)</td>
<td>70 (17)</td>
<td>79 (19)</td>
<td></td>
<td></td>
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<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White, non-Hispanic</td>
<td>294 (35)</td>
<td>139 (33)</td>
<td>155 (38)</td>
<td>.07</td>
<td></td>
</tr>
<tr>
<td>Black, non-Hispanic</td>
<td>341 (42)</td>
<td>185 (44)</td>
<td>156 (38)</td>
<td></td>
<td></td>
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<tr>
<td>Hispanic/Latino</td>
<td>180 (22)</td>
<td>84 (20)</td>
<td>96 (23)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian/Pacific Islander</td>
<td>9 (1)</td>
<td>6 (1)</td>
<td>3 (&lt;1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian/Alaskan native</td>
<td>3 (&lt;1)</td>
<td>0 (0)</td>
<td>3 (&lt;1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subject did not know</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
<td>0 (0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CD4 cell count, median cells/mm(^3) (range)</td>
<td>50 (0–250)</td>
<td>50 (0–209)</td>
<td>52 (0–250)</td>
<td>.92</td>
<td></td>
</tr>
<tr>
<td>Median Karnofsky score (range)</td>
<td>90 (50–100)</td>
<td>90 (60–100)</td>
<td>90 (50–100)</td>
<td>.52</td>
<td></td>
</tr>
<tr>
<td>Antiretroviral treatment</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any antiretroviral</td>
<td>678 (82)</td>
<td>340 (82)</td>
<td>338 (82)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Protease inhibitor</td>
<td>492 (59)</td>
<td>244 (59)</td>
<td>248 (60)</td>
<td>.72</td>
<td></td>
</tr>
<tr>
<td>&gt;=3 Antiretrovirals</td>
<td>151 (18)</td>
<td>76 (18)</td>
<td>75 (18)</td>
<td>.97</td>
<td></td>
</tr>
<tr>
<td>Systemic antibiotic therapy</td>
<td>669 (81)</td>
<td>330 (74)</td>
<td>339 (82)</td>
<td>.33</td>
<td></td>
</tr>
</tbody>
</table>

**NOTE.** Data are no. (% of patients, unless otherwise indicated.

\(^a\) Determined by the \(\chi^2\) test for categorical measurements and Kruskal-Wallis test for ordinal measurements.

administered continuous fluconazole after experiencing frequent episodes of OPC or EC.

**FRIs.** During the study period, only 35 (4.2%) of 829 subjects developed FRIs, 18 (4.3%) of whom were assigned to the episodic treatment arm, and 17 (4.1%) of whom were assigned to the continuous fluconazole arm. There was no significant difference between the study arms with respect to time to development of an FRI (\(P = .97\), by log-rank test). Of these 35 refractory infections, 26 were OPC, and 9 were EC, with 7 refractory EC cases in the continuous fluconazole arm and 2 refractory EC cases in the episodic fluconazole arm (\(P = .09\), by the log-rank test). Two of the 18 subjects with FRIs had initially been randomized to the episodic fluconazole arm and later received continuous fluconazole because of frequent recurrences of OPC or the development of EC. There were 32 FRI episodes during the initial 24 months of follow-up. After 24 months, the specified time used for sample size calculations, the estimated rates (by Kaplan-Meier analysis) of FRI-free survival were 0.952 for the episodic fluconazole arm and 0.944 for the continuous fluconazole arm, indicating no significant difference in the time to FRI between treatment groups (\(P = .88\), by the log-rank test).

**Episodes of OPC and EC.** A greater number of *Candida* infections occurred in the episodic fluconazole arm than in the continuous fluconazole arm. There were 719 episodes of OPC and 16 episodes of EC among subjects in the episodic fluconazole arm, and there were 184 episodes of OPC and 11 episodes of EC among subjects in the continuous fluconazole arm. This equated to a rate of 1.08 and 0.29 episodes of OPC or EC per patient-year in the episodic and continuous fluconazole arms, respectively (\(P < .0001\), by the Z test).

**Invasive fungal infections.** A total of 43 invasive fungal infections, including episodes of EC, were reported (table 2). As expected, there were fewer invasive infections in the continuous fluconazole arm than in the episodic fluconazole arm. A total of 28 episodes of invasive infections occurred among subjects assigned to the episodic fluconazole arm, and 15 episodes of invasive infections occurred among those assigned to the continuous fluconazole arm (\(P = .04\), by the \(\chi^2\) test). Excluding EC, there were 4 invasive systemic fungal infections in the continuous fluconazole arm and 12 invasive infections in the episodic fluconazole arm (\(P = .05\), by the \(\chi^2\) test). Three deaths were attributed to fungal infection in the continuous fluconazole arm, and 1 death was attributed to fungal infection...
in the episodic fluconazole arm; the difference in death rates was not statistically significant.

**Nonfungal opportunistic complications of AIDS.** Episodes of nonfungal opportunistic infections, HIV-related wasting syndrome, or Kaposi sarcoma were recorded for all subjects. A total of 109 events occurred among subjects in the continuous fluconazole arm, and 129 events were reported among those in the episodic fluconazole arm ($P = .33$ by the $\chi^2$ test).

**CD4+ T cell counts for participants.** At baseline, the median CD4+ T cell counts were similar between treatment arms. During the study, both treatment groups demonstrated increases in CD4+ T cell counts (table 3). Interestingly, the median CD4+ T cell count at the last study measurement was 43 cells/mm$^3$ lower for the continuous fluconazole arm, compared with the episodic fluconazole arm ($P = .02$, by the Kruskal-Wallis test).

**Survival.** There were no significant differences in survival between treatment arms. Thirty-one subjects (7%) in the continuous fluconazole arm and 40 subjects (10%) in the episodic fluconazole arm died while receiving their assigned treatments ($P = .28$, by the log-rank test). Including the follow-up of subjects who had discontinued participation in the randomized treatment portion of the study and who continued to be observed for survival, 48 subjects (12%) in the continuous fluconazole arm and 49 subjects (12%) in the episodic fluconazole arm died.

**Laboratory abnormalities on study.** Overall, there appeared to be no significant differences with regard to laboratory abnormalities between groups, with the exception of a platelet count of $<50,000$ platelets/mm$^3$ among persons with initially normal platelet counts. This was seen more frequently in subjects assigned to the continuous therapy fluconazole arm (8...
in the rate of recovery of non-*albicans* Candida species from patients infections by treatment arm.

Isolates were available for 25 of the 35 patients who developed FRIs. The *Candida* species isolated from patients with FRIs included *C. albicans* alone for 18 subjects, *C. albicans* with *C. glabrata* for 5 subjects, *C. glabrata* alone for 1 subject, and *C. glabrata* with *Candida tropicalis* for 1 subject. The median MIC of fluconazole for these isolates was 64 μg/mL (range, <0.25 to ≥256 μg/mL) and did not differ by treatment arm.

The median MIC of fluconazole for the final isolate obtained (regardless of whether infection was present) from subjects was 32 μg/mL for the continuous fluconazole arm and 16 μg/mL for the episodic fluconazole arm (*P* = .0885, by the Kruskal-Wallis arm). The proportion of patients in whom the final candidal isolate was resistant to fluconazole was 50 (45%) of 110 in the continuous fluconazole arm and 79 (36%) of 218 in the episodic fluconazole arm (*P* = .11, by the χ² test).

**DISCUSSION**

To our knowledge, this study represents the largest randomized, controlled, prospective study involving HIV-infected persons designed to examine the risk of FRIs. The incidence of FRIs did not differ significantly by treatment strategy. Although the study did not reach the planned accrual of 948 subjects, the inclusion of 829 subjects, a median follow-up duration of 24 months, and very similar rates of FRIs in both the continuous and episodic fluconazole treatment arms make it unlikely that the study lacked sufficient power to detect a meaningful difference in the incidence of FRIs by treatment assignment. Our study does not support the belief that continuous fluconazole exposure in HIV-infected persons is associated with a significant risk for FRI. Two previous controlled studies found no significant increase in FRIs in subjects who were receiving continuous fluconazole therapy [21, 22]; however, these studies lacked...
power to detect small differences in the rates of FRIs between treatment strategies.

Continuous fluconazole therapy was associated with a higher incidence of thrombocytopenia and smaller increase in CD4+ T cell counts. There was, however, no increase in bleeding or a significant increase in nonfungal opportunistic complications observed in the continuous fluconazole arm. Fluconazole is rarely associated with thrombocytopenia [23–25], and lower CD4+ T cell counts have not been reported for fluconazole [24, 26]. The reasons for finding a greater frequency of thrombocytopenia and lower CD4+ T cell counts for continuous fluconazole recipients remain unclear and may be unrelated to fluconazole use.

In industrialized nations, given the reduction in fungal infections associated with HAART and the lack of a survival benefit associated with continuous fluconazole, the routine use of continuous fluconazole treatment cannot be recommended. However, continuous fluconazole therapy could be considered for individuals experiencing recurrent mucosal infections. In resource-poor settings, where access to HAART is limited, mortality attributed to fungal infections may be considerable [8, 9]. Fluconazole prophylaxis in such a setting has been associated with improved survival rates [9]. In these settings, it is our opinion that the decision to use azole prophylaxis should not be based on a concern for excess risk for FRIs; rather, it should be based on the frequency of mucosal candidiasis and invasive fungal infections.

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