Low-Dose Fluconazole as Primary Prophylaxis for Cryptococcal Infection in AIDS Patients with CD4 Cell Counts of \(\leq 100/mm^3\): Demonstration of Efficacy in a Prospective, Multicenter Trial

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The efficacy of low-dose fluconazole (200 mg orally administered thrice weekly) as primary prophylaxis for cryptococcal infection was prospectively assessed in a multicenter trial involving 218 patients who were infected with human immunodeficiency virus (HIV) and who had CD4 cell counts of \(\leq 100/mm^3\). The median CD4 cell count at baseline was 39/mm\(^3\); 58% of the patients had an AIDS-defining illness or infection prior to enrollment. Cryptococcal meningoencephalitis occurred in 0.4% (1) of the 218 patients. The breakthrough isolate was susceptible to fluconazole, and the fluconazole kinetic study demonstrated adequate drug absorption and serum fluconazole levels; noncompliance could not be excluded in this case. Mucocutaneous and/or esophageal candidiasis developed in 18% (40) of the patients. Noncompliance with fluconazole therapy was the only variable independently associated with breakthrough candidiasis in the study patients \((P = .00002)\). Thus, fluconazole (200 mg thrice weekly) given to HIV-infected patients with CD4 cell counts of \(\leq 100/mm^3\) was efficacious as primary prophylaxis for cryptococcosis, with notably lower costs and increased convenience for patients in comparison with daily administration of the drug.

Disseminated cryptococcal infections occur in 5%–10% of HIV-infected patients and are associated with a mortality of 10%–20% despite therapy. Fluconazole (200 mg orally daily) has been shown to be efficacious as prophylaxis for cryptococcosis in HIV-infected patients with CD4 cell counts of \(<200/mm^3\) [1]. In the National Institutes of Allergy and Infectious Diseases AIDS Clinical Trial Group (ACTG) 981 investigation, fluconazole (200 mg/d) was compared with clotrimazole (10 mg five times daily) as primary prophylaxis for cryptococcosis in patients with CD4 cell counts of \(<200/mm^3\). Cryptococcal infections developed in 0.9% of the patients receiving fluconazole, vs. 7.1% in the clotrimazole group. However, cryptococcosis appears to be rare in patients with CD4 cell counts of \(>100/mm^3\).

Thus, use of fluconazole at higher CD4 cell counts may unnecessarily increase the duration of exposure to fluconazole, with a resultant increase in costs and possibly toxicity. Furthermore, fluconazole has a long half-life (22–48 hours) and may not require daily dosing for primary prophylaxis, a hypothesis also proposed in a retrospective case-control study [2].

In a prospective multicenter trial we sought to determine whether fluconazole (200 mg orally thrice weekly: Monday, Wednesday, and Friday) was efficacious as primary prophylaxis for cryptococcosis in patients with advanced HIV infection (i.e., CD4 cell counts of \(\leq 100/mm^3\)). If found to be efficacious, such a regimen would also be substantially more cost-effective than daily administration of fluconazole. When failure of prophylaxis occurred, the reasons for breakthrough infections—e.g., noncompliance, poor absorption, altered metabolism, or fluconazole resistance—were also sought.

Methods

Between April 1993 and September 1995, consecutive HIV-infected patients with CD4 cell counts of \(\leq 100/mm^3\) were prospectively enrolled at four medical centers in the United States. Patients were excluded if they (1) had a history of cryptococcal infection, (2) were positive for serum cryptococcal antigen at enrollment, (3) had a transaminase level greater than five times the upper limit of normal, or (4) were unable to return for follow-up (e.g., because of incarceration or nonadherence, as defined by a >50% rate of unexplained absences from clinic appointments in the preceding year). The study was approved by the institutional review board at each of the participating institutions.

All patients received fluconazole (200 mg orally) on Mondays, Wednesdays, and Fridays. Study participants underwent clinical and laboratory evaluation (that included a complete blood cell count and liver and renal function tests) at baseline and then every other month. The serum cryptococcal antigen level was determined every 6 months, regardless of symptoms,
in all study patients. Study medication was dispensed to the patients on a monthly basis. Compliance with the study regimen was assessed on each visit by calculation of the proportion of unfilled refills [3] and doses missed each month, as reported by the patient. Patients taking ≥80% of the prescribed drug were considered compliant [4, 5].

The primary endpoint of the study was the development of cryptococcal infection, as revealed by a Cryptococcus neoformans–positive culture (of a specimen from any site) or a positive serum cryptococcal antigen level. Secondary endpoints were occurrences of invasive mucocutaneous candidiasis or other invasive fungal infections. Oropharyngeal candidiasis was defined as a compatible clinical syndrome diagnosed by a positive potassium hydroxide preparation or culture. Esophageal candidiasis required endoscopic diagnosis. The patients were observed until death or discontinuation of fluconazole prophylaxis for any reason.

For patients in whom cryptococcosis developed, a fluconazole-kinetics study and antifungal susceptibility testing were performed to assess whether breakthrough cryptococcal infection was due to antifungal resistance, poor absorption, or accelerated metabolism of fluconazole. For the fluconazole-kinetics study, blood samples were drawn at steady state at 0, 0.5, 1, 2, 3, 4, 6, 8, 12, 16, and 24 hours while the patients were receiving a dose of 200 mg every other day. The serum was frozen at −70°C immediately upon collection. Fluconazole levels were measured in plasma by gas-liquid chromatography [6]. Antifungal susceptibility testing was performed as previously described [7].

Statistical Analyses

Patients’ demographics (e.g., age, CD4 cell counts, HIV risk behavior) and microbiological data were entered into PROPHET statistics (BBN Systems and Technologies, Cambridge, MA). The χ² or Fisher’s exact test was used to compare infection rates. Continuous variables (poor absorption, or accelerated metabolism of) were compared with Student’s t-test or the Mann-Whitney test. A multiple logistic regression model was used to evaluate the effect of several variables on an outcome (candidiasis).

Results

Study Population

A total of 218 patients were enrolled at four sites in the United States between April 1993 and September 1995; the follow-up ended on 31 October 1995. Twelve patients from a fifth site were excluded because of protocol violations at this site. Had these patients been included (constituting <5% of the enrolled patients), the conclusions would have remained unchanged. Ninety-six percent (208) of the 218 patients were male (table 1). The median age was 38 years (range, 21−72 years). Fifty-nine percent (128) of the patients had an AIDS-defining illness or infection (other than a low CD4 cell count) prior to enrollment. The median CD4 cell count at baseline was 39/mm³ (range, 2−100/mm³).

Forty-eight percent (104) of the 218 patients died, and 12% (26) relocated or were lost to follow-up (after a mean of 7.0 months [range, 0.8–23 months]). The mean follow-up for the entire cohort was 12.1 months (range, 0.5–30 months); the mean follow-up for patients who were alive or not lost to follow-up was 14.9 months (range, 2–30 months). Seventy-four percent (162) of the 218 patients were fully compliant with fluconazole throughout the study (i.e., consumed ≥80% of the prescribed doses), 5% (11) were ≥80% compliant (but had at least 1 follow-up cycle in which they were <80% compliant), and 26% (56) were <80% compliant.

Fungal Infections

Cryptococcal infection developed in 0.4% (1) of the 218 patients, and mucocutaneous and/or esophageal candidiasis, in 18% (40). There were no occurrences of invasive mucocutaneous candidiasis or other invasive fungal infections in the study patients.

Cryptococcal Infection

The only case of cryptococcosis involved a patient who presented 30 days after enrollment with headache and ataxia. The patient had a history of brain toxoplasmosis and a CD4 cell count of 7/mm³. Blood and CSF yielded C. neoformans in culture. The patient died 48 days after diagnosis of cryptococcosis; an autopsy also revealed disseminated Mycobact-
Candidiasis

There were 33 cases of oropharyngeal, 5 cases of esophageal, and 2 cases of genital (male) candidiasis among the study patients, for an overall frequency of 18% (40 of 218). The incidence of candidiasis was significantly lower among the patients who were compliant with fluconazole therapy than among those who were noncompliant (10% [17 of 162] vs. 41% [23 of 56]; \( P = .00001 \)). Patients with CD4 cell counts of <50/\( \mu \)L also had a significantly higher incidence of candidiasis (\( P = .05 \)).

In a multivariate analysis in which age, intravenous drug use, homosexuality, CD4 cell count, and noncompliance were entered into the model, only noncompliance with fluconazole was significantly associated with candidiasis (\( P = .00002 \)). When only the compliant patients were analyzed, only a low CD4 cell count (<50/\( \mu \)L) was significantly associated with candidiasis (\( P = .048 \)). Sixty of the study patients were also prescribed rifabutin. Because of possible drug interaction between fluconazole and rifabutin, use of rifabutin could conceivably increase the risk of candidiasis; however, candidiasis developed in 15% (9) of the 60 patients receiving rifabutin and 20% (31) of the 158 patients who did not receive rifabutin (\( P = .42 \)).

Fluconazole susceptibility testing was performed for 17 of the culture-proven cases of breakthrough candidal infections; all cases were due to Candida albicans. For 71% (12) of the 17 C. albicans isolates, the MIC of fluconazole was \( \leq 8 \) \( \mu \)g/mL (range, 0.125-4 \( \mu \)g/mL), and for 29% (5) it was >8 \( \mu \)g/mL (range, 16-32 \( \mu \)g/mL). Fifty-eight percent (7) of the 12 patients for whom the MIC of fluconazole was \( \leq 8 \) \( \mu \)g/mL were compliant with the regimen, as were 60% (3) of the 5 patients for whom the MIC was >8 \( \mu \)g/mL.

Toxicity

Adverse effects attributable to fluconazole were observed in 2% (4) of the 218 study patients: 2 had a rash and 2 experienced nausea. Discontinuation of the fluconazole prophylaxis was required for 2% (4) of the patients, including the two with a rash. For one patient with nausea, the prophylaxis was temporarily withheld and then resumed without incident.

Mortality

Forty-eight percent (104) of the 218 patients died during the follow-up period. The mean time to death after enrollment was 11.0 months (range, 0.5-30 months). Only 1 of 104 deaths was associated with cryptococcal infection; this patient had multiple other opportunistic infections that likely contributed to his demise.

Discussion

Our study differed from that of ACTG 981 [1] in several ways. (1) We targeted for prophylaxis only the HIV-infected patients whose CD4 cell counts were <100/\( \mu \)L. The ACTG 981 study patients had CD4 cell counts of <200/\( \mu \)L (it is interesting that all cases of cryptococcosis in that study involved patients with <100 CD4 cells/\( \mu \)L, and 78% involved those whose counts were \( \leq 50/\mu \)L). (2) We administered fluconazole (200 mg orally) 3 days per week (Monday, Wednesday, and Friday), while the ACTG regimen required administration of 200 mg of fluconazole 7 days per week. (3) We used objective, previously employed criteria to assess medication compliance [3] and correlated compliance with the risk of breakthrough fungal infections in our patients. In the ACTG 981 study, patients’ self-reporting was the only criterion employed to assess study-drug compliance, and no attempt to correlate compliance with cryptococcal or candidal infections was made. (4) Finally, we assessed the susceptibility to fluconazole of cryptococci and candidal species isolates recovered from our patients. Data on antifungal susceptibilities of isolates from breakthrough cryptococcal or candidal infections were not obtained in the ACTG 981 investigation.

In our study, cryptococcal infection developed in 0.46% (1) of our 218 patients; this was slightly lower than the 0.92% (2 of 217) incidence of cryptococcosis in the fluconazole recipients in ACTG 981, despite the fact that our patients had more advanced HIV infection. Fifty-nine percent of our patients had a CD4 cell count of <50/\( \mu \)L as compared with 30% of the ACTG 981 patients. In another study [8], prophylaxis with fluconazole (100 mg daily) was associated with cryptococcosis in 0.3% (1) of the 329 patients with a CD4 cell count of <68/\( \mu \)L. However, the mean duration of follow-up for these study patients was only 161 days, and no attempt to exclude subclinical cryptococcus at baseline (e.g., by assessment of serum cryptococcal antigen) was made [8].

Mucosal candidiasis is a common occurrence in patients with HIV infection. Studies have suggested that up to 90% of patients with HIV infection will experience at least one episode of oropharyngeal candidiasis and 10%–20% will have esophageal candidiasis. The frequency of oropharyngeal candidiasis per 100 patient-years of follow-up was 15.1 in our study (table 2) as compared with 38.1 in patients receiving clotrimazole and 5.7 in patients receiving daily fluconazole in the ACTG 981 study [1]. The higher incidence of breakthrough candidiasis
Table 2. Comparison of cryptococcal and candidal infection rates (given as cases per 100 person-years of follow-up) in this study and the ACTG 981 study [1].

<table>
<thead>
<tr>
<th>Infection</th>
<th>Current study (n = 218)</th>
<th>Fluconazole recipients (n = 217)</th>
<th>Clotrimazole recipients (n = 211)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cryptococcosis</td>
<td>0.45†</td>
<td>0.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Oropharyngeal candidiasis</td>
<td>15.1</td>
<td>5.7</td>
<td>38.1</td>
</tr>
<tr>
<td>Esophageal candidiasis</td>
<td>2.3</td>
<td>0.5</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* The rates of cryptococcosis and esophageal candidiasis were derived from data in the ACTG 981 study report [1], since in that report only the rate for oral candidiasis was provided in terms of the no. of cases per 100 patient-years of follow-up.
† Incidence per 100 person-years of follow-up was calculated as follows: 218 patients were followed for a mean of 12.1 months, or a total of 219 patient-years (218 × 12.1/12 months per year). One cryptococcal infection was observed in these 218 patients, for an incidence of 0.4 cases per 100 patient-years (1/219 × 100).

Among our patients than in the fluconazole recipients of ACTG 981 may imply that daily administration of fluconazole was more effective in preventing candidiasis. A more likely explanation, however, is that a significantly higher proportion of our patients had CD4 cell counts of <50/mm³; low CD4 cell count, particularly <50/mm³, has been identified as a risk factor for candidiasis in a number of studies [9–12].

In our study, noncompliance with fluconazole (P = .0001) and a CD4 cell count of <50/mm³ (P = .05) were significantly associated with breakthrough candidiasis in univariate analysis. When risk factors for candidiasis were analyzed in a multivariate analysis (table 3), only noncompliance was significantly associated with candidiasis (P = .00002). Similar but not identical findings with respect to candidiasis have been reported by Heald et al. [13].

The incidence of oropharyngeal candidiasis was significantly higher among patients who used fluconazole once weekly or sporadically than among patients who received it continuously. Only C. albicans was associated with breakthrough candidiasis in our patients; however, for 29% of the C. albicans isolates, the MIC of fluconazole was >8 μg/mL. This facet of antifungal prophylaxis has been underappreciated; the ACTG 981 study did not assess antifungal resistance in candidal isolates from their patients receiving long-term fluconazole prophylaxis. However, we have shown that emergence of fluconazole-resistant candidiasis may be a potential drawback of sustained prophylaxis.

The compliance of the only patient who contracted cryptococcal meningitis could not be confirmed, as mentioned in the Results section. A precise cutoff for defining fluconazole resistance in cryptococci has not yet been defined; however, the MIC of fluconazole (4 μg/mL) against our patient’s isolate was suggestive of relative susceptibility [14]. The gastrointestinal absorption of fluconazole was adequate, as demonstrated in the kinetics study. A peak fluconazole level of 7.0 μg/mL and a trough level of 1.39 μg/mL were documented while the patient was receiving 200 mg of fluconazole orally every other day. These levels are considered adequate to inhibit cryptococcosis [15–17].

Discontinuation of the fluconazole prophylaxis because of side effects was required for 2% (4) of our 218 patients (predominantly because of skin rashes), as compared with 9% (19) of the 217 patients in the ACTG 981 study (predominantly because of hepatotoxicity).

The issues of cost efficacy must be considered in antifungal prophylaxis. Since we started therapy later in the course of HIV infection and with a lower dosage of fluconazole, it is obvious that the cost of our regimen was notably lower than that of the ACTG 981 study.

One weakness of our study is that it was not a randomized comparative trial. In order to detect a difference in efficacy of 5% with our low-dose regimen (200 mg three times a week) vs. the ACTG 981 regimen (200 mg daily) in a randomized trial, 2,512 patients would have to have been enrolled. Nevertheless, the occurrence of only one failure of prophylaxis (in a patient whose compliance could not be verified) among 218 consecutive patients strongly suggests the efficacy of low-dose fluconazole as prophylaxis for cryptococcal infections in patients with advanced HIV infection.

It is important to note that not a single case of cryptococcal meningitis occurred among 263 patients with CD4 cell counts of 100–200/mm³ in our four study hospitals during the study period, a finding confirming that prophylaxis can be most efficiently directed at those with a CD4 cell count of 100/mm³. Thus, our fluconazole regimen (200 mg thrice weekly for patients whose CD4 cell counts were ≤100/mm³) appears to be as efficacious as the ACTG 981 regimen (200 mg of fluconazole daily for patients whose CD4 cell counts were <200/mm³) as primary prophylaxis for cryptococcosis—with notably lower costs, increased convenience to patients, and fewer serious drug-related adverse effects.

Although prophylaxis with fluconazole in HIV-infected patients has not yet been universally accepted, our data suggest that if one chooses to administer prophylaxis, thrice-weekly fluconazole should be the regimen. Although this regimen is efficacious as prophylaxis for cryptococcosis, it is unknown

Table 3. Multiple-regression analysis of factors associated with candidiasis in the study patients.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.99</td>
<td>0.95–1.00</td>
<td>.75</td>
</tr>
<tr>
<td>Intravenous drug use</td>
<td>1.5</td>
<td>0.55–3.9</td>
<td>.44</td>
</tr>
<tr>
<td>Homosexuality</td>
<td>1.15</td>
<td>0.5–2.8</td>
<td>.75</td>
</tr>
<tr>
<td>CD4 cell count, &lt;50/mm³</td>
<td>1.6</td>
<td>0.7–3.6</td>
<td>.27</td>
</tr>
<tr>
<td>Noncompliance</td>
<td>5.8</td>
<td>2.6–12.9</td>
<td>.00002</td>
</tr>
</tbody>
</table>
whether the rate of resistant *Candida* species is higher with this regimen than with daily prophylaxis. A thrice-weekly dosing schedule is in congruence with other prophylactic strategies (e.g., trimethoprim-sulfamethoxazole as prophylaxis for pneumocystic infection) in HIV-infected patients. By simplification of the prophylactic regimen, treatment adherence would also be facilitated.

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References