Antigen Clearance during Treatment of Disseminated Histoplasmosis with Itraconazole versus Fluconazole in Patients with AIDS

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Disseminated histoplasmosis is a common and serious opportunistic infection among patients with AIDS, especially in areas with a high prevalence of Histoplasma capsulatum infection. Human immunodeficiency virus-infected patients with disseminated histoplasmosis require induction treatment to reverse the clinical illness and suppress the fungal burden in the tissues, followed by chronic maintenance therapy to prevent relapse (3). The standard drug has been amphotericin B, which is both inconvenient and toxic (9, 11). Oral therapy with itraconazole or fluconazole was demonstrated to be effective as induction therapy for patients with mild or moderately severe histoplasmosis in two prospective clinical trials (5, 6). Eligibility criteria, patient selection, and response criteria were designed to be similar for the itraconazole and fluconazole studies to permit assessment of relative effectiveness. In both studies, treatment outcome was assessed by resolution of clinical illness and suppression of fungal burden in the tissues, followed by chronic maintenance therapy to prevent relapse (3). The standard drug has been amphotericin B, which is both inconvenient and toxic (9, 11). Oral therapy with itraconazole or fluconazole was demonstrated to be effective as induction therapy for patients with mild or moderately severe histoplasmosis in two prospective clinical trials (5, 6). Eligibility criteria, patient selection, and response criteria were designed to be similar for the itraconazole and fluconazole studies to permit assessment of relative effectiveness. In both studies, treatment outcome was assessed by resolution of clinical findings, clearance of positive blood cultures, and drug tolerance. Overall, 85% of patients responded to induction with itraconazole versus 74% for fluconazole.

A secondary objective of both studies was to determine the effect of therapy on the clearance rate of Histoplasma antigen from blood and urine. Earlier studies had demonstrated that treatment significantly reduced the antigen concentrations in the blood and urine of patients with histoplasmosis (5, 6). We decided to test the hypothesis that antigen clearance would complement measurements of clinical outcome in assessment of the antifungal activity of new agents for the treatment of histoplasmosis. For this purpose, stored samples from patients in the two treatment studies were tested in the same antigen assay to eliminate interassay variability.

Patient groups. Enrollment into the itraconazole study occurred in 1991 and 1992 (5), followed by the fluconazole study in 1992 and 1993 (6). Study entry required diagnosis of a first episode of disseminated histoplasmosis, as defined previously (5, 6). Patients were excluded if they had severe disease, as defined elsewhere. Treatment regimens and study assessments also were reviewed elsewhere (5, 6).

Histoplasma antigen assay. The test used to detect antigen in serum and urine is an enzyme-linked immunoassay that has been previously described (2). Urine and blood specimens were obtained for measurement of antigen concentrations on enrollment and at weeks 2, 4, 8, and 12 in the fluconazole study and at weeks 1, 2, 4, 8, and 12 in the itraconazole study. Initially, the baseline and week 12 specimens were compared. Analysis of those results prompted a second experiment in which baseline and week 4 specimens were tested. If baseline specimens were unavailable, week 1 specimens were acceptable as replacements. Similarly, if specimens at week 4 were not available, specimens between weeks 4 and 6 were tested, and if specimens at week 12 were not available, the date closest to week 12 between weeks 10 and 20 was used (6). For this analysis of antigen clearance, patients who failed treatment, those with negative results at baseline, and those for whom paired baseline and completion of induction specimens were not available were excluded. For the comparison of baseline and week 4, some cases were excluded because baseline
specimens were exhausted in the prior experiment comparing the baseline and week 12.

**Statistical methods.** Continuous outcomes are presented as mean ± 1 standard deviation and are compared using either Student’s *t* test or the Wilcoxon’s rank sum test. Categorical outcomes are presented as frequency occurring and percentages and are compared using Pearson’s chi-square test for independence. Bonferroni’s procedure was used to adjust *P* values when multiple comparisons were made. A significance level of α = 0.05 was used to test all hypotheses.

The baseline characteristics that may reflect severity of infection were similar between the two studies, except for prior antiretroviral use (Table 1). A higher proportion of subjects in the itraconazole study had received antiretroviral treatment before entry than in the fluconazole study (*P* = 0.006). Nevertheless, CD4 counts were similar, suggesting that immune status was comparable in the two groups. Fungemia cleared more rapidly with itraconazole than with fluconazole (Table 2). At week 4, 92.3% in the itraconazole treatment group had negative fungal blood cultures, which is significantly higher than 61.9% in the fluconazole treatment group (*P* = 0.017). Clearance of fungemia by week 4 of therapy, however, did not predict subsequent response. Of the 38 subjects with negative cultures at week 4 in the fluconazole study, 14 (36.8%) subsequently failed or relapsed, compared to 8 of 17 (47.1%) with fungemia and week 4 in the itraconazole group. Moreover, some of the week 12 specimens were depleted in the second experiment, explaining the reduced number of patients in the comparison of weeks 0 and 4. Furthermore, some of the week 12 specimens were depleted in the first experiment, preventing incorporation of specimens from weeks 0, 4, and 12 in the same assay. Only cases with paired specimens were included. As a consequence, baseline results differ, since not all patients had both week 4 and week 12 specimens and since fewer cases could be examined in the baseline-versus-week 4 analysis. After acknowledgment of these limitations of the analysis of antigen clearance, no differences in clearance were noted with itraconazole versus fluconazole. After 4 weeks of therapy, antigen levels (mean ± 1 standard deviation) in serum fell by 3.46 ± 3.84 U in the itraconazole group (*n* = 10) compared to 2.57 ± 3.65 U in the fluconazole group (*n* = 35) (*P* = 0.5237). Antigen levels in urine fell by 1.30 ± 2.31 U with itraconazole therapy (*n* = 21) versus 0.82 ± 2.80 U with fluconazole therapy (*n* = 41) (*P* = 0.4679). After 12 weeks of therapy, antigen levels in serum fell by 6.26 ± 5.14 U in the itraconazole group (*n* = 33) compared to 5.46 ± 4.81 U in the fluconazole group (*n* = 41) (*P* = 0.4911). Antigen levels in urine fell by 3.16 ± 2.98 U with itraconazole therapy (*n* = 42) versus 3.90 ± 3.22 U with fluconazole therapy (*n* = 44) (*P* = 0.2786).

We have tested the hypothesis that measurement of antigen clearance may be a useful method of comparing the antifungal activity of new medications, having previously shown its promise in studies of experimentally induced histoplasmosis (1). In the animal studies, results of antigen clearance paralleled those of quantitative culture (1).

While nonrandomized studies have assessed the effectiveness of itraconazole (5) and fluconazole (6) for treatment of histoplasmosis, comparative trials have not been possible because of the large sample size required for such a study. However, those studies were developed using similar eligibility criteria with the goal of permitting an assessment of the relative effectiveness of the two agents. As noted in Table 1, the baseline characteristics of the patients in the two studies were comparable, except for prior antiretroviral use. CD4 counts, however, and fungal blood culture positivity were similar in the two studies, suggesting that immune status and severity of histoplasmosis were comparable. Thus, a comparison of the effect of itraconazole and fluconazole therapy on antigen clearance and clearance of fungemia seemed justified.

Clinical response rates to induction therapy were similar in the two studies, 85% with itraconazole and 74% with fluconazole. Although the median time to resolution of fever was 1 week in both studies, weight gain occurred more rapidly with itraconazole (median, 1 week) than fluconazole (median, 4 weeks). Fungemia at week 4 cleared more rapidly with itraconazole than fluconazole (*P* = 0.017). Of note is that culture effectiveness of the two agents. As noted in Table 1, the baseline characteristics of the patients in the two studies were comparable, except for prior antiretroviral use. CD4 counts, however, and fungal blood culture positivity were similar in the two studies, suggesting that immune status and severity of histoplasmosis were comparable. Thus, a comparison of the effect of itraconazole and fluconazole therapy on antigen clearance and clearance of fungemia seemed justified.

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Not all patients had specimens for both analyses, which were conducted at separate times. Furthermore, these baseline results and numbers of patients differ from those in the analysis. The difference in the numbers of patients and median (range) results for week 0 for the comparisons of weeks 0 and 4 and of weeks 0 and 12 is because not all patients had specimens for both analyses, which were conducted at separate times. Furthermore, these baseline results and numbers of patients differ from those in Table 1, which included all subjects who participated in the studies, not only those who could be evaluated for antigen and blood culture clearance.

We recently contrasted clearance of fungemia and antigen in patients treated with itraconazole, described here, versus liposomal amphotericin B (7). Although a combined comparison of liposomal amphotericin B, itraconazole, and fluconazole would have been of interest, liposomal amphotericin B was only given for the first 2 weeks and week 2 blood culture results were not obtained in the fluconazole study. Thus, comparison of clearance of fungal burden during fluconazole versus liposomal amphotericin B would not have been possible. The present study supplements the earlier report and permits us to contrast the clearance of fungemia in these two studies. Accordingly, the following hierarchy of antifungal activity for H. capsulatum emerges: liposomal amphotericin B clears fungemia most rapidly, followed by itraconazole and then fluconazole. Whether clinical response rate would follow that pattern requires a prospective randomized trial, however.

In conclusion, the more rapid clearance of fungemia with itraconazole than fluconazole differs from the similar rate of antigen clearance and suggests that measurement of fungemia provides a better marker for response to therapy than does antigen. Limitations of this study include the fact that the study data were not obtained from a randomized comparison of both therapies and that antigen data were unavailable for several patients. Because of these limitations, we refrain from trying to establish equivalence of the clearance rates even though we failed to show a significant difference between the rates. Prior studies have established the role of antigen detection for the initial diagnosis of histoplasmosis (10) and for evaluation of relapse (8). Antigen levels must be measured at the end of induction therapy, every 3 to 6 months during maintenance therapy, and at the time of suspected relapse to assist in the diagnosis of relapse.

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REFERENCES


