Safety of Discontinuation of Maintenance Therapy for Disseminated Histoplasmosis after Immunologic Response to Antiretroviral Therapy


We performed a prospective observational study to assess the safety of stopping maintenance therapy for disseminated histoplasmosis among human immunodeficiency virus–infected patients after response to antiretroviral therapy. All subjects received at least 12 months of antifungal therapy and 6 months of antiretroviral therapy before entry. Negative results of fungal blood cultures, urine and serum Histoplasma antigen level of <4.1 units, and CD4+ T cell count of >150 cells/mm³ were required for eligibility. Thirty-two subjects were enrolled; the median CD4+ T cell count at study entry was 289 cells/mm³. No relapses of histoplasmosis occurred after a median duration of follow-up of 24 months. This corresponded to an observed relapse rate of 0 cases per 65 person-years. The median CD4+ T cell count at final study visit was 338 cells/mm³. Discontinuation of antifungal maintenance therapy appears to be safe for patients with acquired immunodeficiency syndrome with previously treated disseminated histoplasmosis and sustained immunologic improvement in response to antiretroviral therapy.

Disseminated histoplasmosis is a serious opportunistic infection, occurring in 3%–5% of patients with AIDS living within the areas of endemicity in North America.
CD4+ T cell count to greater than the values associated with the risk of developing the specific opportunistic infection.

On the basis of these observations demonstrating the safety of discontinuing maintenance therapy for other opportunistic infections, we designed a study to assess the safety of discontinuing antifungal maintenance therapy for patients with successfully treated AIDS-related histoplasmosis and response to antiretroviral therapy.

PATIENTS AND METHODS

Study participants. Study subjects had documented HIV infection, previous disseminated histoplasmosis, and documented remission from disseminated histoplasmosis after receiving at least 12 months of antifungal maintenance therapy with systemic antifungals (e.g., itraconazole fluconazole, or amphotericin B). Evidence of previous histoplasmosis was defined as recovery of *Histoplasma capsulatum* from culture; identification of organisms consistent with *H. capsulatum* in stains; or detection of high levels of *Histoplasma* antigen (≥4.1 units) in urine samples, serum samples, or bronchoalveolar lavage fluid.

Remission from disseminated histoplasmosis was defined as the absence of signs, symptoms, or laboratory abnormalities consistent with active disease, *Histoplasma* antigen concentrations of <4.1 units in urine and serum specimens, and a negative result of a fungal blood culture. Subjects were required to have 2 CD4+ T cell counts of ≥150 cells/mm³ obtained within 6 months (performed ≥1 week apart), with one sample obtained within 30 days of entry. Subjects were required to have received antiretroviral therapy for ≥24 consecutive weeks and to be treated with the same regimen for ≥8 consecutive weeks before study entry.

The protocol was open to persons aged ≥13 years who were willing and able to provide informed consent. Subjects aged <18 years required written informed consent of a parent or guardian. Women of childbearing potential were required to have a negative pregnancy test result. Receipt of immunosuppressive medications within 2 months, presence of any acute systemic infection, requirement for continued treatment with systemic antifungal agents, or meningitis or lesions of the brain or spinal cord attributed to histoplasmosis were all exclusionary criteria.

Study end point determinations (relapse of histoplasmosis). Proven relapse of histoplasmosis was defined as a culture positive for *H. capsulatum* or a fungal stain of tissue or body fluid specimens consistent with *H. capsulatum*. Probable relapse of histoplasmosis was defined as the presence of clinical findings suggestive of relapsed histoplasmosis along with a single increase in *Histoplasma* antigen of ≥4.1 units or the demonstration of increases in antigen levels on consecutive testing of ≥4.1 units in the absence of clinical findings.

Routine study procedures. At study entry, subjects discontinued maintenance therapy for disseminated histoplasmosis. Subjects underwent clinical evaluations at 4 weeks, 8 weeks, and every 8 weeks after enrollment. Hematological examination and liver function tests (i.e., determination of aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, bilirubin, and lactate dehydrogenase levels), fungal blood cultures, and serum and urine *Histoplasma* antigen tests were performed at each study visit. Samples for fungal blood cultures (BACTEC Myco/F Lytic) and samples for *Histoplasma* antigen quantitation (Histoplasmosis Reference Laboratory; Indianapolis, IN) were obtained and shipped to centralized reference laboratories at Indiana University Medical Center (Indianapolis).

CD4+ T cell determinations were performed at baseline and every 8 weeks thereafter. Plasma samples were obtained for determination of HIV-1 RNA level at baseline and every 8 weeks thereafter, with testing performed at a centralized laboratory (Johns Hopkins Virology Laboratory; Baltimore, MD) using the UltraSensitive Roche Amplicor HIV-1 Monitor (level of detection, <50 copies/mL) after study completion.

Evaluations for subjects with suspected relapse of histoplasmosis. Subjects with suspected recurrence of histoplasmosis included subjects who developed clinical or routine laboratory findings consistent with histoplasmosis, as well as subjects discovered to have serum or urine *Histoplasma* antigen increases of ≥2 units, compared with the last stable value. Clinical signs and symptoms or routine laboratory results included the following: ≥2 days of temperature ≥38°C; night sweats or diarrhea; weight loss of ≥5% body weight; hepatomegaly; splenomegaly; unexplained lesions of skin, mouth, colon, or brain lesions detected on brain scan; alkaline phosphatase level of ≥2 times the upper limit of normal; development of unexplained anemia (hemoglobin level, <7 g/dL) or thrombocytopenia (thrombocyte level, <50,000/mm³); pulmonary complaints with infiltrates on a chest radiograph; meningitis or focal neurologic complaints; or a sepsis syndrome with hypotension, respiratory failure, coagulopathy, and multiorgan failure. At the time of suspected relapse, physical examination, hematological examination, and liver function tests were performed, blood samples were obtained for fungal culture, and urine and serum samples were obtained for *Histoplasma* antigen quantitation. These studies were repeated every 2–4 weeks up to 3 times, until the findings suggestive of relapsed histoplasmosis resolved or were attributed to another illness or until the diagnosis of relapsed histoplasmosis was confirmed.

Procedures for subjects with a decrease in CD4 count to <100 cells/mm³. If a subject experienced a decrease in the CD4+ T cell count to <100 cells/mm³, an additional CD4+ T cell count was requested within 14 days. If the additional CD4+
T cell count was <100 cells/mm³, the protocol recommended reinstitution of systemic antifungal therapy.

Statistical considerations and study design. At study design, a sample size of 50 subjects was established to provide 80% power to reject a rate of proven or probable relapse of histoplasmosis in subjects discontinuing antifungal maintenance therapy of ≥20% at the 5% level, assuming a “true” relapse rate of 7.5%. The initial study design included a 12-month accrual period and 12 months of follow-up after the last subject was enrolled.

An exact upper 95% binomial CI was constructed for the relapse proportion and an upper 95% Poisson CI was constructed for the incidence rate of histoplasmosis. For all other analyses, 2-sided α = .05 level tests were used. Statistical significance for continuous outcomes was determined with Wilcoxon tests. No adjustment for multiple comparisons was made.

RESULTS

Study subjects. Thirty-two subjects were enrolled in the study from August 1999 through September 2001 at 11 sites in the United States. The study population included 31 men and 1 woman with a median age of 40 years (range, 22–68 years). Fifty-nine percent of subjects were white, 25% were black, and 16% were Hispanic. The median baseline CD4⁺ T cell count was 289 cells/mm³ (range, 124–601 cells/mm³). One subject with a CD4⁺ T cell count of 124 cells/mm³ at baseline had met the eligibility requirements at the time of screening. Fifty-nine percent of the subjects entered the study with HIV loads of <50 copies/mL. All subjects were receiving itraconazole maintenance therapy before enrollment. One subject also reported amphotericin B use, and one other subject received fluconazole early in maintenance treatment. The median duration of antifungal maintenance therapy before study enrollment was 34 months (range, 14–81 months). All 32 subjects were receiving antifungal maintenance therapy without any interruption for >4 weeks in the 12 months before enrollment. At baseline, the median Histoplasma antigen levels were 0.7 units (range, 0.5–2.3 units) for urine and 0.6 units (range, 0.4–0.8 units) for serum.

Study follow-up. After 26 months, an interim review indicated that additional accrual beyond 32 subjects was not necessary to answer the primary study objective. At the time of study completion, 29 subjects were in active follow-up. The median length of follow-up was 24 months (range, 7–35 months), with a total of 65.3 subject-years of follow-up. With the exception of 1 subject who died at week 29 of Staphylococcus aureus sepsis, all remaining subjects were in active follow-up for ≥12 months. Of the other 2 subjects prematurely discontinuing study participation, one was unable to travel to the clinic after week 64, and the other was unable to be contacted after week 94. The subject who died had resumed itraconazole therapy before his death because of the initiation of corticosteroids for a “sarcoidosis-like” illness. This subject’s CD4⁺ T cell count at study entry was 448 cells/mm³, and the last count before death was 529 cells/mm³. This subject had multiple Histoplasma antigen determinations, fungal cultures, histopathologic studies of lung and other tissue samples, and an eventual autopsy, none of which revealed evidence of relapsed histoplasmosis.

Changes in CD4 count and HIV-1 RNA level. Over the course of the study, the CD4⁺ T cell counts of subjects increased from a baseline median of 289 cells/mm³ to 338 cells/mm³ at the final determination. No subject had 2 consecutive CD4⁺ T cell counts of <100 cells/mm³ requiring protocol-mandated reinitiation of antifungal therapy. At baseline, 59% of subjects had HIV-1 RNA levels of <50 copies/mL (range, <50–45,244 copies/mL), and at the last study visit, the HIV-1 RNA level was <50 copies/mL in 81% of subjects.

Study end points. No subject developed either proven or probable histoplasmosis. The observed incidence of relapse was 0 cases per 65.3 person-years of observation (upper 95% CI, 4.6 cases per 100 person-years). The proportion of subjects experiencing relapse was 0 (0%) of 32 (upper 95% CI, 8.94). H. capsulatum was not recovered from any blood culture. Three subjects required additional evaluations for suspected relapse of histoplasmosis. These evaluations were initiated as a result of isolated elevations of Histoplasma antigen levels in urine to >2.0 but <4.1 units for 1 subject and clinical or other laboratory findings for 2 subjects. No subject demonstrated an elevation in serum or urine antigen value of >4.1 units at any time during study follow-up.

DISCUSSION

This study was designed to demonstrate whether discontinuation of maintenance antifungal therapy is safe for AIDS patients with a history of ≥12 months of treatment for disseminated histoplasmosis and immunologic improvement after treatment with antiretroviral therapy. The median study follow-up duration was 24 months, with minimal loss to follow-up. The relapse rate observed during this study was less than the hypothesized rate of 7.5% with 95% confidence. This low relapse rate is in marked contrast to the 60%–80% relapse rates in studies conducted before use of continuous antifungal maintenance therapy and the availability of potent antiretroviral therapy [2]. It is unlikely that cases of relapsed histoplasmosis were overlooked because of the frequency of follow-up visits and use of a Histoplasma antigen test, a test with a high sensitivity for relapsed histoplasmosis in patients with AIDS [18, 19].

Our study required subjects to have completed previous...
induction treatment and a minimum of 12 months of maintenance antifungal therapy. A recent abstract from Argentina reported 39 HIV-infected patients with a response to antiretroviral therapy (CD4+ T cell count >150 cells/mm³) who discontinued antifungal therapy for histoplasmosis after receiving ≥6 months of antifungal maintenance therapy [20]. No relapse was reported after a median duration of follow-up of 16 months. Although discontinuation of antifungal maintenance therapy at a CD4+ T cell count >150 cells/mm³ appears to be safe, the precise level of CD4+ T cells that results in restoration of immunity to histoplasmosis is unknown; it may in fact be lower. The CD4+ T cell count value for reinitiation of antifungal maintenance therapy has also not been defined, but a decrease to <100 cells/mm³ is a reasonable criterion for reinitiation.

In conclusion, this study indicates that it appears safe to discontinue maintenance antifungal therapy for patients with AIDS who have received ≥12 months of antifungal therapy for disseminated histoplasmosis and who experienced sustained immunologic improvement as a result of antiretroviral therapy.

STUDY GROUP MEMBERS

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