

# Comparison of Oral Fluconazole and Itraconazole for Progressive, Nonmeningeal Coccidioidomycosis

## A Randomized, Double-Blind Trial

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**Background:** In previous open-label noncomparative clinical trials, both fluconazole and itraconazole were effective therapy for progressive forms of coccidioidomycosis.

**Objective:** To determine whether fluconazole or itraconazole is superior for treatment of nonmeningeal progressive coccidioid infections.

**Design:** Randomized, double-blind, placebo-controlled trial.

**Setting:** 7 treatment centers in California, Arizona, and Texas.

**Patients:** 198 patients with chronic pulmonary, soft tissue, or skeletal coccidioid infections.

**Intervention:** Oral fluconazole, 400 mg/d, or itraconazole, 200 mg twice daily.

**Measurements:** After 4, 8, and 12 months, a predefined scoring system was used to assess severity of infection. Findings were compared with those at baseline.

**Results:** Overall, 50% of patients (47 of 94) and 63% of patients (61 of 97) responded to 8 months of treatment with fluconazole

and itraconazole, respectively (difference, 13 percentage points [95% CI, -2 to 28 percentage points];  $P = 0.08$ ). Patients with skeletal infections responded twice as frequently to itraconazole as to fluconazole. By 12 months, 57% of patients had responded to fluconazole and 72% had responded to itraconazole (difference, 15 percentage points [CI, 0.003 to 30 percentage points];  $P = 0.05$ ). Soft tissue disease was associated with increased likelihood of response, as in previous studies. Azole drug was detected in serum specimens from all but 3 patients; however, drug concentrations were not helpful in predicting outcome. Relapse rates after discontinuation of therapy did not differ significantly between groups (28% after fluconazole treatment and 18% after itraconazole treatment). Both drugs were well tolerated.

**Conclusions:** Neither fluconazole nor itraconazole showed statistically superior efficacy in nonmeningeal coccidioidomycosis, although there is a trend toward slightly greater efficacy with itraconazole at the doses studied.

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Coccidioidomycosis is a systemic fungal infection caused by *Coccidioides immitis*. Typically, infection stimulates a protective immune response that limits the initial illness and confers lifelong resistance to subsequent infections (1). Occasionally, however, illness progresses, either as a fibrocavitary chronic pneumonia or hematogenously, with dissemination of infection to such extrathoracic sites as the skin, bones, or joints (2, 3). If these complications occur, antifungal therapy is warranted to prevent further tissue destruction and associated morbidity (4).

Azole antifungal agents have become valuable in treating progressive forms of coccidioidomycosis, especially when disease manifestations are not fulminant or immediately life-threatening. Originally, the U.S. Food and Drug Administration approved intravenous miconazole and oral ketoconazole for this indication on the basis of their efficacy and safety (5-14). The lack of an oral form of micon-

azole and untoward effects or drug intolerance related to both agents led to the development of fluconazole, itraconazole, and related congeners. These new drugs have shown therapeutic efficacy against coccidioidomycosis in experimental infections of animals (15-20) and in subsequent clinical trials (21-30).

Our current understanding of optimal management of coccidioid infections is severely limited by the absence of randomized comparative trials that evaluate the different forms of therapy. Multicenter comparative trials are now possible because over the past decade, the evaluation of patients treated for coccidioidomycosis has become standardized. In addition, because of the development of a collaborative group during the same period, trials can now enroll enough patients to support clinically applicable results. In this report, we present the findings from Mycoses Study Group Protocol 20, a comparative trial sponsored by

the National Institute of Allergy and Infectious Diseases that compares two antifungal agents, fluconazole and itraconazole, in the treatment of coccidioidomycosis.

## METHODS

### Patient Eligibility

Patients were considered for enrollment if *C. immitis* was identified by culture, by microscopic examination of infected tissue from outside the lungs, or from respiratory specimens, if a pulmonary infection had persisted for more than 3 months. Patients with HIV infection and pulmonary coccidioidomycosis of shorter duration were eligible if their CD4 count was less than or equal to  $0.25 \times 10^9$  cells/L or if they had diffuse bilateral pneumonia. Enrollees had to be able to take oral medications. Pregnant women were excluded, and women of childbearing potential were required to practice an effective method of birth control. Patients who had received more than 4 mg/kg of body weight of amphotericin B or more than 8 g of an azole antifungal agent for the current episode of infection were ineligible. Other exclusion criteria were immediately life-threatening coccidioidomycosis, presence of coccidioidal meningitis, concomitant administration of a nonstudy systemic antifungal drug, history of hypersensitivity to an azole compound, insufficient evidence of infection on which to assess a response to treatment, renal insufficiency (defined as a serum creatinine concentration  $> 180 \mu\text{mol/L}$  [2.0 mg/dL]), or any of the following abnormal laboratory test values at baseline: hemoglobin level less than 4.3 mmol/L (7 mg/dL), absolute neutrophil count less than  $0.8 \times 10^9$  cells/L, platelet count less than  $0.5 \times 10^9$  cells/L, liver enzyme levels (alanine aminotransferase, aspartate aminotransferase, or alkaline phosphatase) more than 7.5 times the upper limit of normal, or bilirubin level more than 2 times the upper limit of normal. In addition, we excluded patients receiving concomitant medications that could not be managed safely in a blinded study because of potential interactions with the study drugs. The institutional review boards of each participating center approved the study protocol, and signed consent was obtained from each patient before enrollment.

### Randomization and Management of Therapy

This was a double-blind study in which the patient and the investigators were unaware of the identity of the study medications. For patient enrollment, a primary in-

vestigator contacted a central study coordinator, who reviewed the completeness of the patient's eligibility and categorized the major site of infection as chronic pulmonary, soft tissue, or skeletal. Patients in each of the three major categories were randomly assigned to receive fluconazole and itraconazole in a 1:1 ratio. Pharmacists at each participating institution dispensed appropriate medication according to the randomization code that they had been given. The randomization code was stored securely by the pharmacists at each study site, and pharmacists never informed patients, investigators, or other clinical personnel of the patient's designated treatment. Any requests by the primary investigators for unblinding treatment were handled by the principal investigator of the Mycoses Study Group, who was not a collaborating investigator of this study.

The fluconazole tablets (supplied by Pfizer, New York, New York) and itraconazole tablets (supplied by Janssen Pharmaceutica, Piscataway, New Jersey) differed in appearance. Therefore, to maintain blinded treatment, a double placebo design was used. Patients randomly assigned to fluconazole received 400 mg of active fluconazole once daily and placebo itraconazole twice daily. Conversely, patients randomly assigned to itraconazole received 200 mg of active itraconazole twice daily and placebo fluconazole once daily. Therefore, each patient simultaneously received a combination of an experimental study drug and a placebo. Medications were administered orally with meals. Treatment lasted 8 months before the primary outcome assessment and continued for another 4 months to consolidate a response.

### Patient Assessment

At enrollment, all patients provided a complete history, underwent a physical examination, submitted blood specimens for baseline hematologic and chemistry analyses, and were further evaluated with appropriate imaging procedures to determine the extent of evident infection. A central laboratory determined complement-fixing type anticoccidioidal antibodies in serum specimens by using the quantitative immunodiffusion technique (31). Enrolled patients were interviewed and examined at 2 weeks, 4 weeks, 2 months, and every 2 months thereafter while receiving study medication to assess protocol adherence, to determine possible adverse drug effects, and to ensure that the disease was not progressing. Disease activity was as-

sessed at 4, 8, and 12 months. For some patients, especially those with skeletal lesions, computed tomography and magnetic resonance imaging studies were used to assess disease activity.

To assess the extent of infection, we used a previously described scoring strategy (22). In brief, symptoms, appearance of lesions, serum anticoccidioidal antibody titers, and culture results that were repeated during the study were assigned numerical values according to a predefined set of rules. The sum of these values at reassessment during therapy was compared with that determined at enrollment. An increasing score reflected a poorer condition and a decreasing score reflected an improved condition. Response to therapy was defined as a 50% reduction in baseline abnormalities during the first 8 months of therapy. Relapses were considered to have occurred in responding patients who discontinued all antifungal therapy if therapy was reinstated because an existing coccidioidal lesion worsened or a new coccidioidal lesion developed.

#### Determination of Serum Drug Concentrations

Serum specimens were collected from patients 1 month, 4 months, and 8 months after the start of therapy. Specimens were mailed to a central laboratory and stored at  $-70^{\circ}\text{C}$  until protocol therapy was concluded on all patients; all specimens were then assayed at one time. Fluconazole levels were measured by using gas-liquid chromatography (32), and itraconazole levels (itraconazole and hydroxyitraconazole) were measured by using bioassay (33). The lower limit of detection was  $0.2\ \mu\text{g}/\text{mL}$  for fluconazole and  $0.5\ \mu\text{g}/\text{mL}$  for itraconazole.

#### Statistical Analysis

The primary null hypothesis, which we hoped to reject, was that the efficacy of fluconazole and itraconazole after 8 months of treatment was equal in favor of the alternative hypothesis (at least 20% superiority of one treatment). Past studies on nonmeningeal progressive coccidioidomycosis indicated that between 55% and 65% of patients should respond to 400 mg of either azole drug per day (22, 29). With a response rate of 55%, a two-sided type I error of 5%, and a power of 0.8, 196 patients would be required to show a 20% difference in the efficacy of the two treatments. We planned to enroll 4 additional patients to accommodate any ineligible cases; therefore, accrual was to be 200 patients. Enrollment was closed with 198 pa-

tients after reaching a termination date that had been agreed to in advance by the pharmaceutical sponsors, the Mycoses Study Group, and the National Institutes of Health.

The primary outcome analysis was performed on an intention-to-treat basis at 8 months on all patients, regardless of whether they reached an end point or discontinued the protocol prematurely. For treatment to be considered successful, a patient had to be evaluated at 8 months and have a score less than or equal to 50% of the baseline score. Patients who did not meet these criteria were considered to be nonresponding. Consolidation therapy continued for 4 months to complete 1 year of protocol treatment.

Two interim analyses were performed during the trial. The levels of significance maintained an overall  $P$  value of 0.05 and were calculated according to the O'Brien-Fleming stopping boundaries. This final analysis used a  $Z$  score of 1.985 with an associated  $P$  value of 0.0471 (34).

The treatment groups were compared by using the Kruskal-Wallis test for ordinal measurements and the chi-square test for categorical measurements (35). The Fisher exact test was used for efficacy comparisons. Since several patients were treated for less than 1 year, the probabilities of early treatment termination and their standard errors were estimated by using techniques of survival analysis, and the treatment groups were compared by using the log-rank test (36). The logistic regression model was used for multivariate assessment of the relative risk for successful response during therapy, after adjustment for potential confounders (37). Baseline data associated with a successful outcome at 8 and 12 months in univariate analyses ( $P < 0.3$ ) were initially included with the patient's treatment regimen in the multivariate model. Univariate efficacy subgroup analyses were performed separately for each disease category. There were too few patients in each category to perform meaningful multivariate analysis.

We used StatXact 4 for Windows (Cytel Software, Cambridge, Massachusetts) for efficacy comparisons that involved exact methods. All other statistical analyses were done by using SAS software, version 6.12 (SAS Institute, Inc., Cary, North Carolina).

#### Role of the Funding Sources

Pharmaceutical sponsors provided support for patient care costs. The Mycoses Study Group performed data management and study analysis.

**Table 1. Enrollment in Each Treatment Group, according to Collaborating Study Site**

Study Site	Location	Fluconazole Group	Itraconazole Group	All Patients
		(n = 97)	(n = 101)	
		<i>n</i>		<i>n</i> (%)
University of Arizona	Tucson, AZ	34	33	67 (34)
University of California, San Diego	San Diego, CA	26	25	51 (26)
Kern Medical Center	Bakersfield, CA	12	11	23 (12)
Santa Clara Valley Medical Center	San Jose, CA	11	12	23 (12)
Maricopa Medical Center	Phoenix, AZ	7	9	16 (8)
University of Texas at San Antonio	San Antonio, TX	4	7	11 (5)
University of Southern California	Los Angeles, CA	3	4	7 (3)

## RESULTS

### Characteristics of Patients at Enrollment

Between 25 November 1992 and 4 February 1997, seven collaborating sites enrolled 198 patients in the study. Ninety-seven patients were randomly assigned to receive fluconazole, and 101 were randomly assigned to receive itraconazole (Table 1). Combined enrollment from all sites was steady throughout this period, with accrual averaging 48 patients per year. Six of the enrolled patients were considered ineligible because the evaluable disease was insufficient for meaningful assessment (2 patients in each treatment group) or because a mycologic diagnosis could not be satisfactorily established (1 patient in each group). A seventh enrolled patient who was fully eligible was removed from the study because his health maintenance organization would not allow him to participate while remaining a member. Therefore, 191 patients form the basis of our report.

The demographic characteristics of the study patients are summarized in Table 2. The median age was 38 years (range, 6 to 81 years), and 73% of the patients were men. Sixty-six patients (35 in the fluconazole group and 31 in the itraconazole group) had at least one preexisting condition that may have predisposed them to progressive infection. Allocation to therapy did not significantly differ for any demographic characteristic.

The major sites of infection and the associated symptoms are shown in Table 3. Eighteen patients with both soft tissue and skeletal lesions, 5 of whom also had pulmonary lesions, were assigned to the skeletal group. Pulmonary cavities (one of which had ruptured, resulting in a pyopneumothorax) were present in 24 patients. Of patients with skeletal infections, 42 had bony involvement (10 with multiple bones) and 10 had joint involvement (1 with multiple joints). Vertebral lesions were present in 14 pa-

tients, and 9 patients had debridement of skeletal lesions as part of management. These characteristics were similar in both treatment groups. In addition to the most common

**Table 2. Characteristics of Study Patients\***

Characteristic	Fluconazole Group (n = 94)	Itraconazole Group (n = 97)	Total Patients (n = 191)
Median age, y	37	39	38
Men, %	74	71	73
Ethnicity, %			
White	44	37	40
Hispanic	32	34	33
Black	16	19	17
Asian	4	2	3
Pacific Islander	0	4	2
Native American	1	0	1
Other	3	4	7
Previous treatment, %	48	45	47
Preexisting conditions, %	35	31	66
Diabetes mellitus	16	12	28
Corticosteroid therapy	9	6	15
Alcoholism	4	5	9
Immunosuppressive therapy	3	5	8
Coronary artery disease or congestive heart failure	1	6	7
Lymphoma or Hodgkin disease	2	6	8
AIDS or AIDS-related complex	4	1	5
HIV infection but no AIDS or AIDS-related complex	1	1	2
Chronic obstructive pulmonary disease, cor pulmonale, asthma	3	2	5
Anemia	1	3	4
Radiation therapy for malignant conditions	2	2	4
Renal insufficiency	0	2	2
Renal transplantation	1	0	1
Myelodysplastic syndrome	1	0	1
Sarcoidosis	1	0	1
Hepatitis	1	0	1
Pulmonary tuberculosis	0	1	1

\* For all characteristics,  $P > 0.2$ .

**Table 3. Major Categories of Disease and Principal Associated Symptoms\***

Variable*	Fluconazole Group	Itraconazole Group	All Patients	P Value
	← n →			
All patients	94	97	191	
Fatigue	49	53	102	>0.2
Weight loss	26	32	58	>0.2
Decreased appetite	13	28	41	0.01
Fever	26	30	56	>0.2
Night sweating	27	22	49	>0.2
Chills/rigor	7	5	12	>0.2
Arthralgia	10	12	22	>0.2
Myalgia	5	8	13	>0.2
Patients with pulmonary infection	35	35	70	
Cough	29	30	59	>0.2
Sputum production	18	21	39	>0.2
Hemoptysis	9	10	19	>0.2
Pleuritic chest pain	9	6	15	>0.2
Shortness of breath	14	18	32	>0.2
Patients with skeletal infection	27	23	50	
Bone or joint pain	26	23	49	>0.2
Local swelling	18	16	34	>0.2
Local erythema	6	4	10	>0.2
Drainage	6	4	10	>0.2
Decreased range of motion	3	3	6	>0.2
Patients with soft tissue infection	32	39	71	
Local pain	23	26	49	>0.2
Swelling	25	29	54	>0.2
Drainage	4	12	16	0.04
Erythema	5	9	14	>0.2

\* Symptoms that constituted less than 5% of the total were not included.

systemic symptoms of fever, weight loss, and fatigue, other symptoms included myalgia (13%), arthralgia (22%), and headache (7%). Only decreased appetite and drainage from soft tissue lesions were unevenly distributed; both were more frequent in patients receiving itraconazole. Twenty-two hematologic and blood chemistry analyses were done at the beginning of therapy, but the results did not differ significantly between treatment groups.

The distribution of abnormalities, physical lesions, serologic characteristics, and fungal growth at the time of enrollment are shown in **Figure 1**. The major contributions to each patient's total score were derived from symptoms and from the appearance of the specific sites of infection. Cultures were not used to assess response to therapy in most patients because they were initially obtained by surgical biopsy, bronchoscopy, or another invasive procedure and were unlikely to be repeated after a diagnosis had been established. Although adjunctive debridement proce-

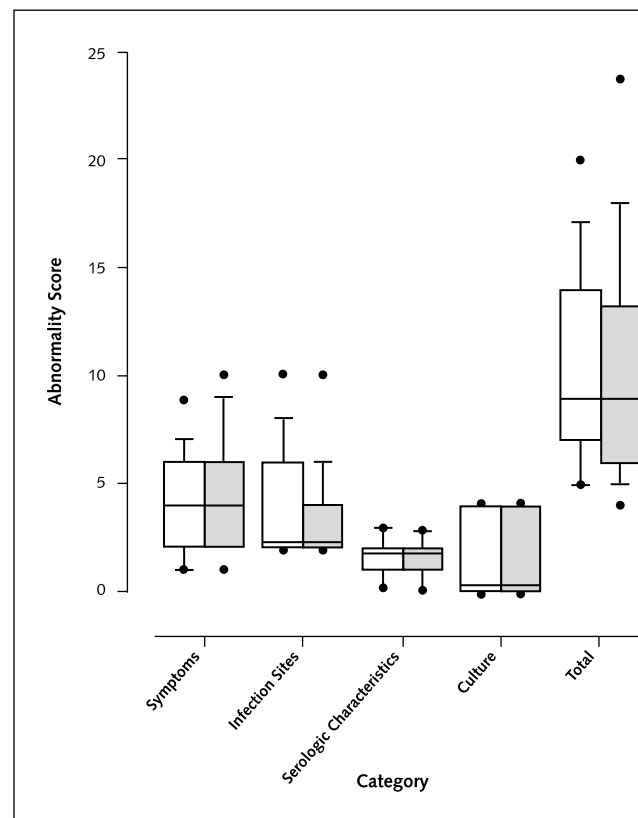
dures were allowed in the protocol at the discretion of the treating physicians, only 6 of 94 patients in the fluconazole group (6.4%) and 4 of 97 patients in the itraconazole group (4.1%) had surgery to manage coccidioidal lesions ( $P > 0.2$ ).

### Response to Therapy

The flow of patients during the entire course of protocol therapy is shown in **Figure 2**. Twenty-seven fluconazole-treated patients (28%) and 19 itraconazole-treated patients (20%) terminated therapy before 8 months ( $P = 0.07$  [log-rank test]). Treatment-related causes were identified in 9 fluconazole-treated patients (10%) and 9 itraconazole-treated patients (9%). All patients who stopped therapy before 8 months were considered nonresponders for the primary end point.

Overall, 47 of 94 patients (50%) responded to flucon-

**Figure 1. Box plots of baseline abnormalities associated with coccidioidal infection in patients treated with fluconazole (white bars) or itraconazole (gray bars).**



Center lines represent the median value. Error bars indicates the 5th and 95th percentiles, and dots represent individual results that fall outside these ranges.

**Table 4. Patients Who Responded to Treatment after 8 and 12 Months, according to Category of Disease\***

Variable	Fluconazole Group	Itraconazole Group	P Value
	n/n (%)		
8 months			
All patients	47/94 (50 [40–60])	61/97 (63 [52–72])	0.08
Patients with pulmonary infection	19/35 (54 [37–71])	20/35 (57 [39–74])	>0.2
Patients with soft tissue infection	21/32 (66 [47–81])	29/39 (74 [58–87])	>0.2
Patients with skeletal infection	7/27 (26 [11–46])	12/23 (52 [31–73])	0.08
12 months			
All patients	54/94 (57 [47–68])	70/97 (72 [62–81])	0.04
Patients with pulmonary infection	22/35 (63 [45–79])	23/35 (66 [48–81])	>0.2
Patients with soft tissue infection	22/32 (69 [50–84])	31/39 (79 [64–91])	>0.2
Patients with skeletal infection	10/27 (37 [19–58])	16/23 (70 [47–87])	0.03

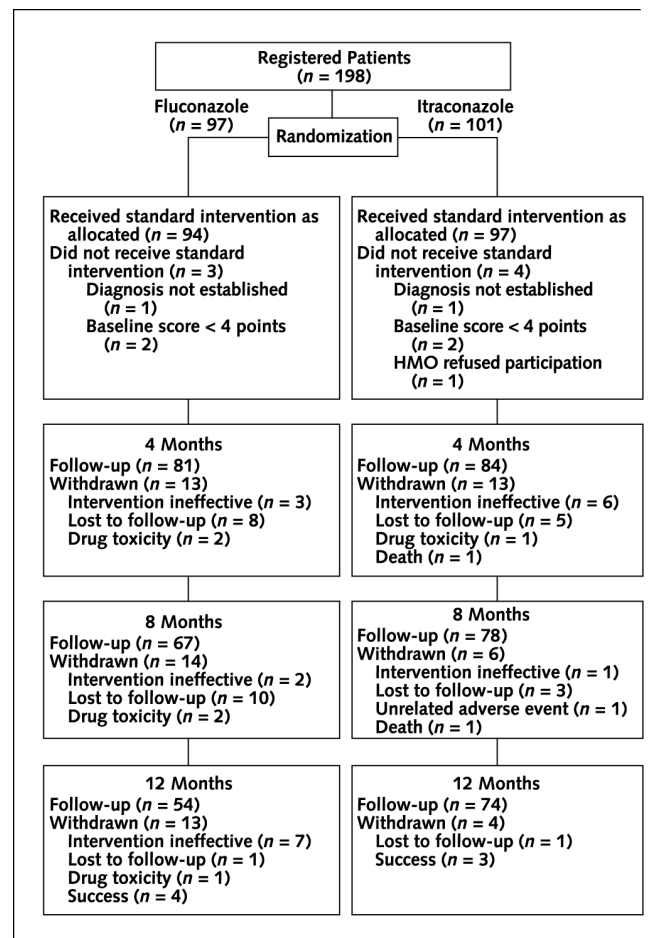
\* Numbers in square brackets are 95% CIs.

azole and 61 of 97 patients (63%) responded to itraconazole, a difference of 13 percentage points (95% CI, –2 to 28 percentage points;  $P = 0.08$ ) that did not allow us to reject the null hypothesis (Table 4). All three of the subgroups classified by primary site of infection showed a trend for superiority of itraconazole. This trend was most striking in patients with skeletal infections: At 8 months, the proportion of responders in the itraconazole group (12 of 23 patients [52%]) was two times greater than that in the fluconazole group (7 of 27 patients [26%]).

The response to fluconazole and itraconazole over the entire course of protocol therapy is shown in Figure 3. For analysis at 12 months, 7 patients (4 responding to fluconazole and 3 responding to itraconazole) were considered to have sustained their response although treatment was discontinued or their 12-month evaluation was incomplete. Comparison of responses at 8 months and 12 months showed that the number of responding patients in the itraconazole group had increased from 61 of 97 to 70 of 97 (72%) as the result of continued improvement in 13 and worsening in 4. In contrast, response of patients in the fluconazole group increased from 47 of 94 to 54 of 94 (57%) as the result of continued improvement in 8 and discontinuation of therapy in 1 because of apparent drug toxicity. Therefore, after 12 months, the difference between the two treatment groups was 15 percentage points (CI, 0.003 to 30 percentage points;  $P = 0.05$ ).

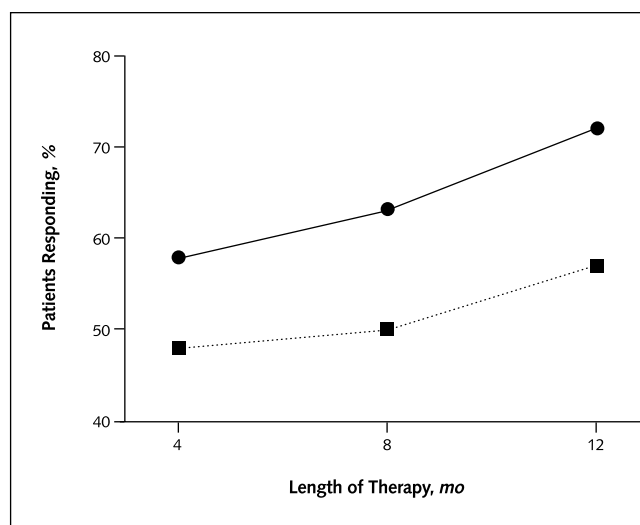
Responses to treatment were also analyzed in relation to serum drug concentrations at 1, 4, and 8 months of therapy. Of patients receiving fluconazole, 65 had 3 specimens analyzed, 18 had 2 specimens analyzed, and 7 had 1 specimen analyzed. Of patients receiving itraconazole, 75 had 3 specimens analyzed, 12 had 2 specimens analyzed, and 6 had 1 specimen analyzed. Median serum levels  $\pm$  SE

for patients at each of the three time points were  $21.2 \pm 1.3 \mu\text{g/mL}$  ( $n = 88$ ),  $17.8 \pm 1.6 \mu\text{g/mL}$  ( $n = 83$ ), and  $16.5 \pm 1.2 \mu\text{g/mL}$  ( $n = 65$ ) for fluconazole

**Figure 2. Flow of patients through the study.**

HMO = health maintenance organization.

**Figure 3.** Patients responding after different mean durations of protocol therapy with fluconazole (dotted line) or itraconazole (solid line).



and  $7.3 \pm 0.5 \mu\text{g/mL}$  ( $n = 86$ ),  $8.1 \pm 0.6 \mu\text{g/mL}$  ( $n = 77$ ), and  $6.7 \pm 0.7 \mu\text{g/mL}$  ( $n = 68$ ) for itraconazole. When responding and nonresponding patients in the two treatment groups were compared for the distribution of the median, highest, or lowest drug concentrations, no statistically significant differences were seen. For all patients in whom serum drug concentrations were measured, only 3 (1 treated with itraconazole and 2 treated with fluconazole) had undetectable concentrations in all specimens. The patient receiving itraconazole had 3 specimens assayed, and the 2 patients receiving fluconazole had 3 and 2 specimens assayed. All 3 patients were evaluated as responding patients.

Baseline characteristics were analyzed for association with response to either therapy. Soft tissue infections, no previous therapy for coccidioid infection, more than four symptoms, and lack of dermal erythema overlying skeletal lesions seemed to be independently associated with re-

sponse at 8 months (Table 5). After 12 months of treatment, only soft tissue infection and no previous therapy demonstrated a persistent independent association. However, at this later assessment, the association of itraconazole with response was also apparent. Other baseline factors that did not seem to be independently associated with response were age, sex, ethnicity, preexisting diseases, specific symptoms, and numerous specific laboratory tests.

#### Occurrence of Relapse after Discontinuation of Therapy

After 12 months of protocol therapy, antifungal therapy was discontinued in 86 patients who were considered responding patients by their clinicians. The abnormality score decreased by at least 50% in 85 of these patients; 1 patient's score was 60% of baseline, but the treating clinician was satisfied with the degree of response. No further follow-up was available for 18 patients. Of the remaining 68 patients, relapse occurred in 8 of 29 who received fluconazole (28%) and 7 of 39 who received itraconazole (18%) ( $P > 0.2$  [log-rank test]). Relapses occurred from 31 to 497 days after cessation of therapy, and follow-up for nonrelapsing patients ranged from 46 to 519 days.

Thirty-nine patients in whom treatment was considered a success at 12 months continued to receive commercially obtained azole therapy (fluconazole, itraconazole, or ketoconazole) as directed by their treating physicians. One of these patients also received treatment with amphotericin B. Patients who did or did not continue therapy differed significantly in the likelihood of baseline weight loss (46% vs. 24%;  $P = 0.02$ ), baseline shortness of breath (27% vs. 9%;  $P = 0.02$ ), median baseline antibody titer (1:32 vs. 1:8;  $P = 0.003$ ), and median number of baseline local abnormalities (11 vs. 9;  $P = 0.04$ ). Also, the median 12-month antibody titer differed significantly (1:2 vs. 1:1;  $P = 0.003$ ). These differences suggest that patients who continued treatment had more extensive illness. However, the two groups did not seem to differ with respect to treat-

**Table 5.** Multivariate Analysis of Baseline Factors Associated with Response after 8 and 12 Months of Treatment

Factor	Odds Ratio after 8 Months of Treatment (95% CI)	P Value	Odds Ratio after 12 Months of Treatment (95% CI)	P Value
Soft tissue infection	3.4 (1.7–7.0)	<0.001	2.2 (1.1–4.3)	0.026
First course of treatment	2.9 (1.5–5.6)	0.0011	2.9 (1.5–5.6)	<0.001
>4 symptoms	1.3 (1.1–1.5)	<0.001	–	–
Lack of dermal erythema overlying skeletal lesions	8.1 (1.3–50.0)	0.0242	–	–
Itraconazole regimen	1.5 (0.8–2.9)	0.19	1.9 (1.0–3.6)	0.05

ment regimen, age, sex, ethnicity, concomitant immunosuppressive therapy, or any of 20 other specific signs and symptoms analyzed.

### Drug Tolerance and Adverse Events

All patients, regardless of eligibility status, were evaluated for drug tolerance and adverse events (drug-related or non–drug-related). Serious adverse events occurred in 8 of 97 fluconazole-treated patients (8% [CI, 4% to 16%]) and 6 of 101 itraconazole-treated patients (6% [CI, 2% to 12%]) ( $P > 0.2$ ). Three adverse events could have been caused by the study drug: elevated liver enzyme levels (1 itraconazole-treated patient), hypokalemia (1 itraconazole-treated patient), and vomiting (1 fluconazole-treated patient). Two deaths in itraconazole-treated patients (2%) were attributed to underlying disease (sepsis associated with chemotherapy-induced neutropenia and cardiac arrest). Death from cardiac arrest occurred in a third patient who was randomly assigned to receive itraconazole but never began protocol therapy because of ineligibility. Other serious events that were not considered drug-related included elevated liver enzymes (1 patient in each treatment group), hypokalemia (1 patient in the itraconazole group), and gastrointestinal symptoms (1 patient in the fluconazole group). Eight other patients (6 treated with fluconazole and 2 treated with itraconazole) were withdrawn from the study because of mild to moderate symptoms, such as rash (fluconazole group), dry skin (fluconazole group), nausea (fluconazole group), or difficulty concentrating (itraconazole group). The relationship of these events to the study drug is uncertain. Of interest, alopecia was reported in 15 of 97 patients receiving fluconazole (15%) and only 4 of 101 patients receiving itraconazole (4%) ( $P = 0.01$ ). This confirms previous reports that suggest an association between fluconazole and hair loss (21, 38). Similarly, dry lips were reported in 11 of 97 patients receiving fluconazole (11%) and in 0 of 101 patients receiving itraconazole ( $P = 0.008$ ). Dry skin and cheilitis have previously been reported with fluconazole therapy (39).

### DISCUSSION

Our study was designed to determine whether 8 months of fluconazole or itraconazole treatment was a more effective therapy for progressive forms of coccidioidomycosis. Although it is estimated that 100 000 coccidio-

idal infections occur in the United States per year (40), only a small proportion of patients develop progressive forms of the disease and would therefore be eligible for enrollment in this study. Seven treatment centers collaborated for more than 4 years to accrue the number of patients needed to adequately test our primary hypothesis. This study also required a method to assess or score responses in groups of patients who manifested wide spectra of signs, symptoms, and anatomic lesion sites. We used a predefined scoring system to compare patients' responses at intervals during therapy with their responses at initiation of treatment (22, 29). Only the collaborative multicenter approach and the practical assessment procedures that are now available allowed us to perform this study and obtain the results presented here.

Rigorous dichotomous analysis of our primary end point (response rates after 8 months of treatment) suggests but does not demonstrate superior efficacy of itraconazole ( $P = 0.08$ ). Our data indicate with 95% confidence that differences in efficacy at 8 months could range from 2% higher for fluconazole-treated patients to 28% higher for itraconazole-treated patients. Because our findings show that the response rate was only 13 percentage points higher in itraconazole-treated patients, we are unable to reject the statistical null hypothesis. By 12 months of therapy, itraconazole seemed to be slightly superior. It has been noted previously that protracted durations of treatment are required before a clinical response can be detected (30). Our results should be considered tentative and should be interpreted with caution.

In subgroup analyses, skeletal infections tended to respond better to either 8 or 12 months of itraconazole treatment than to similar durations of fluconazole treatment. Compared with previous studies, this result does not seem to be caused by an unusually better response rate with itraconazole. Graybill and colleagues (29) used the same procedures for evaluating response and reported that 54% of patients with skeletal lesions (6 of 11 patients) responded to itraconazole, compared with 52% in our study. In contrast, the response of skeletal infections to fluconazole in our study (26% [CI, 11% to 46%]) is lower than that in an open-label nonrandomized trial by Catanzaro and coworkers (22), who noted a response in 12 of 14 patients with skeletal lesions (86% [CI, 49% to 98%]). In our study, patients with skeletal infections were similar with respect to baseline characteristics regardless of treatment group (data not shown), indicating that infections

were not disproportionately more severe in fluconazole-treated patients. It is possible that the discrepancy between our study and that of Catanzaro and coworkers in response rates for skeletal infections is caused by chance alone, given the relatively small numbers of patients in the latter report. Alternatively, it is possible that treating physicians have developed increased familiarity with azole therapy for coccidioidal infections over the past several years and were more willing to enroll patients with difficult infections in our study than in past studies.

In a post hoc analysis, four baseline characteristics seemed to be independently associated with an increased likelihood of response (Table 5). The improved response of soft tissue infection compared with infection at other sites has been seen in previous studies and in fact motivated us to stratify patients according to disease category. Moreover, failure of subsequent fluconazole or itraconazole treatment seemed more likely in patients in whom previous therapy had failed. Both of these factors were associated with outcome at 12 and 8 months of treatment. Associations with the other two factors (more numerous symptoms and lack of dermal erythema overlying skeletal lesions) were evident only in the earlier analysis. Further studies will be needed to clarify their significance.

Itraconazole absorption has been recognized as variable (41) and has been less predictable than fluconazole absorption in other studies. Therefore, we believed that it was important to assess serum levels to determine whether responses were less likely if serum levels were low. Eighty-eight of 90 fluconazole-treated patients (98%) and 92 of 93 itraconazole-treated patients (99%) had at least one serum specimen with detectable drug concentrations. Drug was detected in all specimens for 92% of patients in each group (83 of 90 patients receiving fluconazole and 86 of 93 receiving itraconazole). All but 3 patients (2 in the fluconazole group and 1 in the itraconazole group) had detectable drug in at least one of three specimens. Therefore, it seems that adherence to therapy was good. However, we found no association between low serum levels and decreased response to therapy with either drug. Although our data do not explain this lack of correlation, the practical conclusion is that monitoring serum levels for patients treated for coccidioidal infections with either azole drug is not routinely necessary. Exceptions to this general guideline might include patients who are prescribed itraconazole and have hypochlorhydria or enteropathy, patients in whom adherence is a concern, or patients who are taking concomitant

medications that may reduce absorption or hasten itraconazole metabolism (42).

The frequency of relapse after discontinuation of therapy was similar in the fluconazole and itraconazole groups, and the 18% relapse rate after itraconazole therapy is almost the same as the 15% to 16% reported previously (29, 30). The 28% relapse rate after fluconazole therapy is lower than but not inconsistent with that reported by Catanzaro and coworkers (22) (39% [CI, 16% to 63%]). It should also be noted that treating physicians were unwilling to discontinue treatment in 39 of 125 patients who were considered to have responded after 12 months of protocol therapy. Patients who continued treatment beyond the protocol therapy were significantly more likely to have evidence of more extensive infection at baseline (for example, weight loss, shortness of breath, higher baseline antibody titers, and more numerous local abnormalities) than those who did not. If all patients had discontinued therapy at the end of protocol treatment, it is likely that the overall relapse rates would have been higher. These findings emphasize the fact that therapy for coccidioidomycosis must be improved in order to reduce relapse rates.

Management of individual patients with different forms of coccidioidomycosis varies according to such factors as the risk for complications, the location of specific lesions, and the rate of disease progression (4). Our study gives clinicians more information on which to base their choice of azole therapies. Our results indicate a trend toward superiority of itraconazole, especially in patients with skeletal lesions. However, this pattern must be weighed against potential difficulties with absorption and drug interactions, which may limit the usefulness of itraconazole for some patients. An intravenous form of itraconazole, which has recently been approved for clinical use, may negate some of these problems. However, it is important to note that we studied only a single dosage of fluconazole (400 mg/d). Higher dosages seem to be more effective for some patients with coccidioidal meningitis (24), and this could also be the case in patients with nonmeningeal coccidioidal infections (21), such as those in our study. Although both itraconazole and fluconazole can be recommended for treatment of coccidioidomycosis, the differences between them increase the available options for management.

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## References

1. Stevens DA. Coccidioidomycosis. *N Engl J Med*. 1995;332:1077-82.
2. Drutz DJ, Catanzaro A. Coccidioidomycosis. Part II. *Am Rev Respir Dis*. 1978;117:727-71.
3. Stevens DA. Coccidioidomycosis: A Text. New York: Plenum Medical Book; 1980:1-279.
4. Galgiani JN, Ampel NM, Catanzaro A, Johnson RH, Stevens DA, Williams PL. Coccidioidomycosis. Treatment guidelines. *Clin Infect Dis*. 2000;30:658-61.
5. Stiller RL, Defelice R, Brass C, Galgiani JN, Stevens DA. Therapy of cutaneous coccidioidomycosis with imidazoles: comparison of results with miconazole and ketoconazole. In: Proceedings of the Fifth International Conference on the Mycoses. Superficial, Cutaneous, and Subcutaneous Infections, 27-30 April 1997, Caracas, Venezuela. Washington, DC: Pan-American Health Organization; 1980:375-81.
6. Stevens DA, Stiller RL, Williams PL, Sugar AM. Experience with ketoconazole in three major manifestations of progressive coccidioidomycosis. *Am J Med*. 1983;74:58-63.
7. Brass C, Galgiani JN, Campbell SC, Stevens DA. Therapy of disseminated or pulmonary coccidioidomycosis with ketoconazole. *Rev Infect Dis*. 1980;2:656-60.
8. Craven PC, Graybill JR, Jorgensen JH, Dismukes WE, Levine BE. High-dose ketoconazole for treatment of fungal infections of the central nervous system. *Ann Intern Med*. 1983;98:160-7.
9. Harrison HR, Galgiani JN, Reynolds AF Jr, Sprunger LW, Friedman AD. Amphotericin B and imidazole therapy for coccidioidal meningitis in children. *Pediatr Infect Dis*. 1983;2:216-21.
10. DeFelice R, Galgiani JN, Campbell SC, Palpant SD, Friedman BA, Dodge RR, et al. Ketoconazole treatment of nonprimary coccidioidomycosis. Evaluation of 60 patients during three years of study. *Am J Med*. 1982;72:681-7.
11. Graybill JR, Lundberg D, Donovan W, Levine HB, Rodriguez MD, Drutz DJ. Treatment of coccidioidomycosis with ketoconazole: clinical and laboratory studies of 18 patients. *Rev Infect Dis*. 1980;2:661-73.
12. Catanzaro A, Einstein H, Levine B, Ross JB, Schillaci R, Fierer J, et al. Ketoconazole for treatment of disseminated coccidioidomycosis. *Ann Intern Med*. 1982;96:436-40.
13. Ross JB, Levine B, Catanzaro A, Einstein H, Schillaci R, Friedman PJ. Ketoconazole for treatment of chronic pulmonary coccidioidomycosis. *Ann Intern Med*. 1982;96:440-3.
14. Galgiani JN, Stevens DA, Graybill JR, Dismukes WE, Cloud GA. Ketoconazole therapy of progressive coccidioidomycosis. Comparison of 400- and 800-mg doses and observations at higher doses. *Am J Med*. 1988;84:603-10.
15. Clemons KV, Stevens DA. Efficacies of two novel azole derivatives each containing a morpholine ring, UR-9746 and UR-9751, against systemic murine coccidioidomycosis. *Antimicrob Agents Chemother*. 1997;41:200-3.
16. Lutz JE, Clemons KV, Aristizabal BH, Stevens DA. Activity of the triazole

- SCH 56592 against disseminated murine coccidioidomycosis. *Antimicrob Agents Chemother.* 1997;41:1558-61.
17. Clemons KV, Homola ME, Stevens DA. Activities of the triazole SCH 51048 against *Coccidioides immitis* in vitro and in vivo. *Antimicrob Agents Chemother.* 1995;39:1169-72.
  18. Fierer J, Kirkland T, Finley F. Comparison of fluconazole and SDZ89-485 for therapy of experimental murine coccidioidomycosis. *Antimicrob Agents Chemother.* 1990;34:13-6.
  19. Clemons KV, Hanson LH, Perlman AM, Stevens DA. Efficacy of SCH39304 and fluconazole in a murine model of disseminated coccidioidomycosis. *Antimicrob Agents Chemother.* 1990;34:928-30.
  20. Defaveri J, Sun SH, Graybill JR. Treatment of murine coccidioidal meningitis with SCH39304. *Antimicrob Agents Chemother.* 1990;34:663-4.
  21. Diaz M, Negroni R, Montero-Gei F, Castro LG, Sampaio SA, Borelli D, et al. A Pan-American 5-year study of fluconazole therapy for deep mycoses in the immunocompetent host. Pan-American Study Group. *Clin Infect Dis.* 1992;14(Suppl 1):S68-76.
  22. Catanzaro A, Galgiani JN, Levine BE, Sharkey-Mathis PK, Fierer J, Stevens DA, et al. Fluconazole in the treatment of chronic pulmonary and nonmeningeal disseminated coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med.* 1995;98:249-56.
  23. Pérez JA Jr, Johnson RH, Caldwell JW, Arsura EL, Nemecheck P. Fluconazole therapy in coccidioidal meningitis maintained with intrathecal amphotericin B. *Arch Intern Med.* 1995;155:1665-8.
  24. Galgiani JN, Catanzaro A, Cloud GA, Higgs J, Friedman BA, Larsen RA, et al. Fluconazole therapy for coccidioidal meningitis. The NIAID-Mycoses Study Group. *Ann Intern Med.* 1993;119:28-35.
  25. Diaz M, Puente R, de Hoyos LA, Cruz S. Itraconazole in the treatment of coccidioidomycosis. *Chest.* 1991;100:682-4.
  26. Tucker RM, Denning DW, Dupont B, Stevens DA. Itraconazole therapy for chronic coccidioidal meningitis. *Ann Intern Med.* 1990;112:108-12.
  27. Catanzaro A, Fierer J, Friedman PJ. Fluconazole in the treatment of persistent coccidioidomycosis. *Chest.* 1990;97:666-9.
  28. Tucker RM, Galgiani JN, Denning DW, Hanson LH, Graybill JR, Sharkey K, et al. Treatment of coccidioidal meningitis with fluconazole. *Rev Infect Dis.* 1990;(12 Suppl 3):S380-9.
  29. Graybill JR, Stevens DA, Galgiani JN, Dismukes WE, Cloud GA. Itraconazole treatment of coccidioidomycosis. NIAID Mycoses Study Group. *Am J Med.* 1990;89:282-90.
  30. Tucker RM, Denning DW, Arathoon EG, Rinaldi MG, Stevens DA. Itraconazole therapy for nonmeningeal coccidioidomycosis: clinical and laboratory observations. *J Am Acad Dermatol.* 1990;23:593-601.
  31. Wieden MA, Galgiani JN, Pappagianis D. Comparison of immunodiffusion techniques with standard complement fixation assay for quantitation of coccidioidal antibodies. *J Clin Microbiol.* 1983;18:529-34.
  32. Harris SC, Wallace JE, Foulds G, Rinaldi MG. Assay of fluconazole by megabore capillary gas-liquid chromatography with nitrogen-selective detection. *Antimicrob Agents Chemother.* 1989;33:714-6.
  33. Hostetler JS, Heykants J, Clemons KV, Woestenborghs R, Hanson LH, Stevens DA. Discrepancies in bioassay and chromatography determinations explained by metabolism of itraconazole to hydroxyitraconazole: studies of interpatient variations in concentrations. *Antimicrob Agents Chemother.* 1993;37:2224-7.
  34. Lan KK, DeMets DL. Discrete sequential boundaries for clinical trials. *Biometrika.* 1983;70:659-63.
  35. Snedecor GW, Cochran WG. *Statistical Methods.* 6th ed. Ames, IA: Iowa State Univ Pr; 1967.
  36. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *Journal of the American Statistical Association.* 1958;53:457-81.
  37. Hosmer DW Jr, Lemeshow S. *Applied Logistic Regression.* New York: J Wiley; 1989.
  38. Pappas PG, Kauffman CA, Perfect J, McKinsey DS, Bamberger DM, et al. Alopecia associated with fluconazole therapy. *Ann Intern Med.* 1995;123:354-7.
  39. Williams PL, Billys M, Morrison J. Severe cheilitis associated with high-dose fluconazole [Abstract]. In: Einstein H, Catanzaro A, eds. *Coccidioidomycosis. Proceedings of the Fifth International Conference on Coccidioidomycosis, Stanford, California, 24-27 August 1994.* Washington, DC: National Foundation for Infectious Diseases; 1996:423.
  40. Galgiani JN. Coccidioidomycosis: a regional disease of national importance. Rethinking approaches for control. *Ann Intern Med.* 1999;130:293-300.
  41. Denning DW, Tucker RM, Hanson LH, Stevens DA. Treatment of invasive aspergillosis with itraconazole. *Am J Med.* 1989;86:791-800.
  42. Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. *Drugs.* 1989;37:310-44.