

## A RANDOMIZED TRIAL OF ITRACONAZOLE IN ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS

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### ABSTRACT

**Background** Allergic bronchopulmonary aspergillosis is a hypersensitivity disorder that can progress from an acute phase to chronic disease. The main treatment is systemic corticosteroids, but data from uncontrolled studies suggest that itraconazole, an orally administered antifungal agent, may be an effective adjunctive therapy.

**Methods** We conducted a randomized, double-blind trial of treatment with either 200 mg of itraconazole twice daily or placebo for 16 weeks in patients who met immunologic and pulmonary-function criteria for corticosteroid-dependent allergic bronchopulmonary aspergillosis. A response was defined as a reduction of at least 50 percent in the corticosteroid dose, a decrease of at least 25 percent in the serum IgE concentration, and one of the following: an improvement of at least 25 percent in exercise tolerance or pulmonary-function tests or resolution or absence of pulmonary infiltrates. In a second, open-label part of the trial, all the patients received 200 mg of itraconazole per day for 16 weeks.

**Results** There were responses in 13 of 28 patients in the itraconazole group (46 percent), as compared with 5 of 27 patients in the placebo group (19 percent,  $P=0.04$ ). The rate of adverse events was similar in the two groups. In the subsequent open-label phase, 12 of the 33 patients who had not had a response during the double-blind phase (36 percent) had responses, and none of the patients who had a response in the double-blind phase of the trial had a relapse.

**Conclusions** For patients with corticosteroid-dependent allergic bronchopulmonary aspergillosis, the addition of itraconazole can lead to improvement in the condition without added toxicity. (N Engl J Med 2000;342:756-62.)

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**A**LLERGIC bronchopulmonary aspergillosis is a hypersensitivity disease of the lungs that is almost always caused by *Aspergillus fumigatus* (Table 1). Several sets of diagnostic criteria have been proposed,<sup>2-4</sup> incorporating the clinical, immunologic, and radiographic features of the disease, since no single test is sufficiently discriminating. Allergic bronchopulmonary aspergillosis is underdiagnosed; prospective studies indicate that 7 to 14 percent<sup>5</sup> of patients (or more<sup>6</sup>) with corticosteroid-dependent asthma meet the generally accepted definitions, as do 6 percent of patients with cystic fibrosis.<sup>7</sup>

The disease can progress from the acute phase to stages characterized by exacerbations and corticosteroid dependency and finally to end-stage fibrotic disease.<sup>8</sup>

Therapy for allergic bronchopulmonary aspergillosis involves prophylaxis against and treatment of acute exacerbations as well as prevention of end-stage fibrotic disease. Systemic corticosteroids are the mainstay of therapy, despite the fact that supportive data have come from uncontrolled trials involving small numbers of patients.<sup>9-12</sup> The long-term benefits of corticosteroids are unclear, and their many side effects are well known. In addition, there is a small possibility of invasive aspergillosis.<sup>13,14</sup> These problems have led to a search for alternative treatments. It has been hypothesized that reducing the fungal burden in the respiratory tract would decrease chronic antigenic stimulation, reduce the inflammatory response, ameliorate symptoms, and possibly reduce the long-term risk of progression or slow progression. Studies of treatment with five inhaled or oral antifungal agents have reported limited success.<sup>15-22</sup>

More recently, itraconazole, an orally administered triazole that is highly active in vitro against aspergillus,<sup>23</sup> has been studied in nonrandomized trials of patients with allergic bronchopulmonary aspergillosis,<sup>24-27</sup> with promising results. Treatment led to a lowering of the corticosteroid dose; improved pulmonary function, exercise tolerance, symptoms, and radiographic features; and reduced IgE concentrations. The improvement was maximal after three to six

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**TABLE 1.** CHARACTERISTICS OF ALLERGIC BRONCHOPULMONARY ASPERGILLOSIS.

Episodic airway obstruction (asthma) and wheezing
Immediate wheal-and-flare reaction to aspergillus antigen on skin testing
Precipitating antibodies or other IgG antibodies against aspergillus antigens
Elevated total serum IgE concentration
Presence of aspergillus-specific serum IgE, particularly when patients are symptomatic
Eosinophils in sputum and blood
Episodic fever and pulmonary infiltrates
Nonsegmental and transient, with a clinical presentation of eosinophilic pneumonia and asthma
Segmental, with blocking of bronchi by plugs
Brown flecks (fungal elements) in sputum, mucous plugs (often containing fungal elements), or cultures positive for aspergillus
Other radiographic findings of bronchial inflammation or central bronchiectasis*
Ring markings or parallel shadows
Band or glove-finger shadows due to a bronchus filled with mucus
Upper-lobe fibrosis (a late finding)

\*Data are from McCarthy et al.<sup>1</sup>

months of treatment. Nevertheless, these results may not have represented true improvement, because of the variable and episodic course of the disease. We undertook the present randomized, double-blind, placebo-controlled clinical trial to address some of these questions.

**METHODS**

**Study Design**

The study of patients with allergic bronchopulmonary aspergillosis had two phases. The first phase was a double-blind comparison of itraconazole at the dose most commonly prescribed for the treatment of deep mycoses, 200 mg twice daily, and an identical-appearing placebo over a 16-week period. The second phase involved open-label treatment of all patients with a smaller dose of itraconazole (200 mg daily) for another 16 weeks, to assess the effects of this dose and of long-term treatment. This regimen reflected patients' feedback during the design of the study.

Dynamic randomization permitted balanced distribution of patients in the two groups at each center according to various prognostic factors, including the stage of disease.<sup>28</sup> Study drugs were randomly assigned numbers in blocks and arbitrarily distributed among sites. Randomization was performed at a central location, according to site, and each patient was assigned a medication number on entry. The patients were scheduled to be stratified according to the presence or absence of cystic fibrosis, but no patients with cystic fibrosis enrolled. Treatment assignments were not available either to investigators or to patients during or after the trials.

**Patients and Procedures**

Because several different definitions of allergic bronchopulmonary aspergillosis have been published,<sup>2,4</sup> the definition used as a criterion for entry was determined by prospectively polling 16 participating centers. A strict definition was selected (Table 2), with the idea that subsequent studies could examine outcomes in more loosely defined groups of patients. The institutional review board at each center approved the study, and all patients gave written informed consent before enrollment.

Patients were instructed to take their study medication with food, and if antacids became necessary, to take the antacids two hours before or after the study medication. Compliance was assessed by counting the pills remaining at clinic visits.

**TABLE 2.** CRITERIA FOR ENTRY INTO AND EXCLUSION FROM THE STUDY.\*

<b>Entry criteria†</b>
Asthma (defined as a ratio of forced expiratory volume in one second to forced vital capacity <0.7) within 2 weeks before entry
Aspergillus-specific IgE within 2 weeks before entry‡
Total serum IgE concentration >400 IU per milliliter within 2 weeks before entry (or >250 IU per milliliter, with evidence of fluctuation with disease activity)§
Dependence on corticosteroid therapy (need for ≥10 mg of prednisone or equivalent per day orally) within 2 weeks before entry¶
Documented history of immediate reaction to aspergillus antigen on skin testing
Documented history of pulmonary infiltrates characteristic of allergic bronchopulmonary aspergillosis
History of IgG antibody against aspergillus documented by any method**
<b>Exclusion criteria</b>
Treatment with itraconazole for ≥5 days within 2 months before entry
Use of any other antifungal agents within 14 days before entry
Treatment with any investigational drug either concurrently or within 1 month before entry
Pregnancy or lactation
Serum aspartate aminotransferase, alanine aminotransferase, or alkaline phosphatase concentrations >5 times the normal concentration or bilirubin concentration >2 mg per deciliter (34 μmol per liter)
Use of rifampin, rifabutin, phenobarbital, phenytoin, carbamazepine, astemizole, terfenadine, histamine H <sub>2</sub> blockers, or omeprazole or continual use of antacids
History of hypersensitivity to azole compounds
An age <13 years and weight <40 kg
Unreliability in following physicians' directives
Inability to take oral medication

\*For enrollment, patients had to meet all seven entry criteria. Patients were excluded if they met at least one of the exclusion criteria.

†A history of eosinophilia (absolute eosinophil count, >500 per cubic millimeter) or of sputum production with brown flecks was not required for entry but was recorded in many patients.

‡The radioallergosorbent test (CAP, Pharmacia, Kalamazoo, Mich., or 3M EAST, Bio-Whittaker, Walkersville, Md.) was used for the detection of IgE.

§Measurements of IgE were performed at least in duplicate by enzyme-linked immunosorbent assay at dilutions of 1:10 and 1:100 (Immugenex, Palo Alto, Calif.).

¶The definition of Berlinger<sup>29</sup> was used.

||Characteristic infiltrates are described in Table 1.

\*\*For patients with no history of IgG antibody against aspergillus, blood samples were screened for IgG precipitins (direct immunoassay kit, Greer, Lenoir, N.C.) in response to antigens from *Aspergillus fumigatus* serotypes 1 and 2, and if the results were negative, with antigens from *A. fumigatus* serotype 3, *A. flavus*, *A. glaucus*, *A. nidulans*, and *A. niger* (Immugenex).

Hematologic and other laboratory tests, described in detail previously,<sup>30</sup> were performed at the time of entry and every eight weeks thereafter to identify adverse effects. Coagulation and erythrocyte sedimentation assays were deemed not routinely warranted. Chest radiographs were obtained at study entry, and the presence or absence of bronchiectasis was determined radiographically. Chest radiographs were subsequently performed every 8 weeks for 32 weeks. Culturing of sputum for aspergillus, assessment of exercise tolerance (number of steps taken in a 10-minute walk at maximal speed and measured with a pedometer), and pulmonary-function tests (forced expiratory volume in one second, forced vital capacity, forced expiratory flow in the midexpiratory phase [at 25 to 75 percent of total volume], peak flow rate, and carbon monoxide diffusing capacity) were performed at the time of study entry and at 16 and 32 weeks.

Use of the study medication was to be discontinued if any variable assessed by liver-function testing increased to more than

5 times the base-line value or increased to 2.5 to 5 times the base-line value and remained greater than 2.5 times the base-line value after the study medication had been withheld for five days, if nausea or vomiting occurred and was considered intolerable or prevented oral intake despite treatment with antiemetics for five days, or if a rash appeared and worsened over the course of five days or signs of exfoliation appeared.

The susceptibility of aspergillus isolates to itraconazole was performed by broth macrodilution, as previously described.<sup>23,31</sup> According to published data on serum itraconazole concentrations attainable with usual doses,<sup>23,32,33</sup> isolates were deemed susceptible to itraconazole if both the minimal inhibitory concentration and the minimal fungicidal concentration were less than or equal to 6.25  $\mu\text{g}$  per milliliter, resistant if both were greater than 6.25  $\mu\text{g}$  per milliliter, and tolerant if the minimal inhibitory concentration was less than or equal to 6.25  $\mu\text{g}$  per milliliter and the minimal fungicidal concentration was greater than 6.25  $\mu\text{g}$  per milliliter. The concentration of 6.25  $\mu\text{g}$  per milliliter represents the minimal inhibitory concentration for 95 percent of isolates; 84 of 88 isolates in a previous study had minimal inhibitory concentrations at or below this value.<sup>23</sup> The results were not available to the investigators during the trial.

### Response Criteria

Response criteria for the double-blind phase of the trial were defined by consensus before the study (Table 3). If any response data were missing at week 16, it was assumed that the criteria for those responses had not been met.

During the initial 16-week trial, investigators were required to attempt to taper the doses of corticosteroids used by the patients, beginning after 4 weeks. For patients who were receiving at least 10 mg of prednisone or its equivalent per day at entry and during the trial, the dose was to be reduced by not more than 50 percent every four weeks; once patients began receiving less than 10 mg per day, the dose was to be reduced to zero over a period of at least four weeks.

Nine aspects of physical and mental health — physical function, physical and emotional health, social function, pain, mental health, vitality, general health perceptions, and changes in health perceptions — were assessed at weeks 0, 16, and 32 with use of the 36-item Medical Outcomes Study Short-Form General Health Survey (SF-36).<sup>34</sup> Scores on each aspect can range from 0 (worst) to 100 (best).

Response criteria used for the open-label phase were the same as those used for the double-blind phase, except that there was no requirement for tapering of the corticosteroid dose since this was to have been done or attempted during the double-blind phase. Responses were assessed at week 32.

For patients who had a response during the double-blind phase of the trial, relapse during the open-label phase (weeks 16 to 32) was defined as a return to their base-line (week 0) values. Specifically, relapse was considered to have occurred when it became necessary to double the corticosteroid dose because of a return of symptoms, when there was a 33 percent increase in the IgE concentration, and when one of the following occurred: a 33 percent decrease in exercise tolerance, a 33 percent decrease in any of the variables measured by pulmonary-function testing, or the appearance of any new pulmonary infiltrates that may be seen in allergic bronchopulmonary aspergillosis.

### Statistical Analysis

Outcomes were assessed according to the intention-to-treat principle. The null hypothesis was that no difference in the response rate would be found between the two groups during the first 16 weeks of the trial (the double-blind phase). We estimated that 27 patients per group would be required, given an estimated response rate of 40 percent in the itraconazole group and a response rate of 5 percent or less in the placebo group,<sup>24-26</sup> for the study to have a power of 80 percent to detect an absolute difference in response of 35 percent, with a type I error of 0.05. To allow for a dropout

**TABLE 3.** DEFINITION OF A RESPONSE IN THE DOUBLE-BLIND TRIAL.\*

Reduction in the dose of corticosteroid by 50 percent or more
Decrease in the total IgE concentration by 25 percent or more
At least one of the following
Increase in exercise tolerance by at least 25 percent
Improvement by 25 percent in results of at least one of five pulmonary-function tests†
Resolution of infiltrates present at enrollment and attributable to allergic bronchopulmonary aspergillosis and no subsequent development of infiltrates, or absence of development of any infiltrates during the study if no infiltrates were present at enrollment‡

\*Patients were considered to have had a response if they met the first two criteria and at least one of the conditions of the third. Responses were assessed by comparing values at week 0 with those at week 16.

†The following were assessed: forced expiratory volume in one second, forced vital capacity, forced expiratory flow in the midexpiratory phase, peak flow rate, and carbon monoxide diffusing capacity.

‡Characteristic infiltrates are described in Table 1.

rate of up to 20 percent, we set the enrollment level at 68 patients (34 per group).

An internal monitoring board, assembled by the National Institute of Allergy and Infectious Diseases and comprising investigators knowledgeable in the methods of clinical trials, the study of mycoses, or both, reviewed the progress of the trial. This board convened twice during the study. On the first occasion the members were supplied with individual patient outcomes and adverse effects in a blinded fashion. On the second occasion they performed an interim analysis after 44 patients had completed the double-blind phase. The interim analysis used a group sequential method incorporating the Lan-DeMets use function with the O'Brien-Fleming boundaries for early stopping of the study to reject the null hypothesis.<sup>35</sup> In addition, the board analyzed each of the study groups to determine whether one had a disproportionate number of adverse effects or even a few instances of serious effects. No cause for early closure of the study was found. The enrollment goal was not met. The study concluded short of the desired enrollment because the rate accrual was slower than expected.

Fisher's exact test was used to compare the groups with respect to sex, race, and response and relapse rates. Wilcoxon's rank-sum test was used to compare the groups with respect to age and quality of life. A P value of less than 0.05 was assumed to indicate statistical significance. All reported P values are two-sided. Because a conservative spending function was used for the interim analysis, the nominal (unadjusted) P values are reported.

## RESULTS

### Base-Line Characteristics of the Patients

For the double-blind phase of the trial, 28 patients were randomly assigned to receive itraconazole and 27 to receive placebo at 13 centers. The two groups were not significantly different with respect to most base-line characteristics (Table 4), stage of allergic bronchopulmonary aspergillosis, the presence or distribution of concomitant diseases, and the quality of life, as assessed by the SF-36. However, the ratio of women to men was higher in the itraconazole group than in the placebo group ( $P=0.03$ ).

### Outcomes in the Double-Blind Phase

The rate of response to therapy was significantly higher in the itraconazole group than in the placebo

**TABLE 4.** BASE-LINE CHARACTERISTICS OF THE PATIENTS.\*

CHARACTERISTIC	ITRACONAZOLE GROUP (N=28)	PLACEBO GROUP (N=27)	P VALUE
Age (yr)	48±16	54±12	
Race or ethnic group (no. of patients)			
White	24	22	
Black	1	3	
Hispanic	3	2	
Sex (M/F)	10/18	18/9	0.03
Bronchiectasis (no. of patients)	13	12	
Characteristic pulmonary infiltrates (no. of patients)†	6	6	
Forced expiratory volume in 1 sec (liters)	1.6±0.7	1.8±0.6	
Forced vital capacity (liters)	2.5±1.0	2.9±0.7	0.09
Forced expiratory flow in the midexpiratory phase (liters/sec)	1.2±0.9	1.2±0.9	
Carbon monoxide diffusing capacity (ml/min/mm Hg)	20.3±4.6	22.0±5.4	
Peak flow rate (liters/min)	221±142	260±165	
Exercise tolerance (no. of steps taken in 10 min)	888±364	797±333	
Completion of study regimen (no. of patients)	25	25	

\*Plus-minus values are means ±SD.

†Characteristic infiltrates are described in Table 1.

group (P=0.04) at the end of the initial 16-week phase of the trial. After adjustment for the interim analysis, the results remained significant (P=0.048). Response rates were greater in the itraconazole group than in the placebo group for four of the five components of the definition of a response (Table 5). Tests of pulmonary function also showed that, overall, the itraconazole group had greater improvements in forced expiratory volume in one second, forced vital capacity, forced expiratory flow in the midexpiratory phase, and peak flow rate than the placebo group; the carbon monoxide diffusing capacity was the exception. In some instances it was unclear whether the physicians had truly attempted to reduce the dose of corticosteroids as the study guidelines required. Since a reduction in the corticosteroid dose of at least 50 percent was one of the criteria for a response, lack of an attempt to reduce the dose would lower the response rates.

Subcategories of the population were also analyzed for response. Patients without bronchiectasis, regardless of group assignment, had a greater overall response rate than those with bronchiectasis (43 percent vs. 20 percent). Among patients in the itraconazole group, 60 percent of those without bronchiectasis had a response, as compared with 31 percent of those with this condition (and 8 percent of those with bronchiectasis in the placebo group). A logistic-regression model was used to evaluate the effects of several fac-

**TABLE 5.** RATES OF RESPONSE OVERALL AND ACCORDING TO SEX, AGE, AND BASE-LINE CORTICOSTEROID DOSE.\*

VARIABLE	ITRACONAZOLE GROUP	PLACEBO GROUP	P VALUE
	no. with response/total no.		
Overall response	13/28	5/27	0.04
Decrease in corticosteroid dose	17/22	14/25	
Decrease in total IgE	15/25	11/25	
Increase in exercise tolerance	7/21	4/21	
Improvement in ≥1 pulmonary-function tests	15/24	11/24	
Resolution or absence of characteristic pulmonary infiltrates†	18/22	18/23	
Sex‡			
Male	5/10	3/17	
Female	8/16	2/8	
Age			
≥50 yr	8/12	3/14	0.045
<50 yr	5/16	2/13	
Base-line dose of prednisone or equivalent			
≤12.5 mg/day	6/10	3/15	
>12.5 mg/day	5/16	2/11	

\*Denominators indicate the numbers of patients for whom data were available.

†Characteristic infiltrates are described in Table 1.

‡One female patient and one male patient in the placebo group and two female patients in the itraconazole group who left the study early because of adverse events are not included in the numbers shown for this variable.

tors on the response rate. Only the treatment group was significantly associated with a response (P=0.03; odds ratio for the itraconazole group as compared with the placebo group, 3.8); there were no significant associations between response and sex (P=0.8; odds ratio for women as compared with men, 0.7), corticosteroid dose (P=0.3; odds ratio for those taking >12.5 mg per day at base line as compared with those taking ≤12.5 mg per day, 0.7), or age (P=0.1; odds ratio for subjects ≥50 years old as compared with those <50 years old, 2.3).

There were no significant differences between the two groups in the absolute scores on the subscales of the SF-36 at 16 weeks or in aggregate changes in individual scores for eight of the nine items. Patients receiving placebo had a greater improvement in the score on the vitality subscale than did patients in the itraconazole group (P=0.03).

**Adverse Events**

Adverse events occurred in 25 of the 28 patients in the itraconazole group (89 percent) and 23 of the 27 patients in the placebo group (85 percent). There were no significant differences between the groups in the results of hematologic or laboratory tests when the results were analyzed according to the World Health Organization toxicity scale (in which a score of 1 indicates mild adverse effects and a score of 4 life-threatening effects).<sup>36</sup> Serious adverse events, as defined by

the Food and Drug Administration,<sup>37</sup> occurred in two patients in the itraconazole group (cardiomyopathy and fatal cardiac arrest in one and upper respiratory tract infection with fever and increased sputum production in the other) and in two patients in the placebo group (fever and increased sputum production in one and acute exacerbation of asthma necessitating intubation in the other). None of these events were considered related to use of the study drug. In addition to the patient who died, two patients in the itraconazole group discontinued treatment (one because of pregnancy and the other because of constipation and nausea), as did two patients in the placebo group (one because of abnormal liver-function tests and the other because of urticaria). Events presumed to be related to treatment occurred in five patients in the itraconazole group (hair loss, dry mouth, hand tremors, increased perspiration, gastritis, loose bowel movements, constipation, forgetfulness, increased fatigue, and stomach cramps) and in four patients in the placebo group (leg rash, hypokalemia, leg edema, dry skin, and breast swelling).

#### Outcomes in the Open-Label Phase

Of the 55 patients who were enrolled in the double-blind phase of the trial, 50 proceeded to the open-label phase, during which they received 200 mg of itraconazole once daily. Of 33 patients who had not had a response during the double-blind phase, 12 (36 percent) had a response to open-label itraconazole. This included 4 of 13 patients who received itraconazole in the double-blind phase (31 percent) and 8 of 20 who received placebo (40 percent). None of these response rates were significantly different from the response rate of 46 percent in the itraconazole group during the double-blind phase. The 40 percent rate of response to itraconazole among patients who had previously received placebo was much higher than the response to placebo during the double-blind phase (19 percent,  $P=0.007$ ), suggesting that itraconazole had an actual treatment effect.

Scores on the SF-36 at the end of the open-label phase did not differ significantly between the patients originally assigned to the itraconazole group and those originally assigned to placebo on all nine subscales. Changes in the scores on eight subscales during the open-label phase did not differ significantly between the original groups; however, scores on the vitality subscale improved to a significantly greater extent in the group originally assigned to itraconazole than in the original placebo group ( $P=0.03$ ), the reverse of what was seen in the double-blind phase.

No relapses occurred during open-label treatment with itraconazole among the 12 patients who had had a response to itraconazole and the 5 who had had a response to placebo during the double-blind phase.

#### Susceptibility in Vitro

Eleven isolates from sputum cultures obtained from 10 patients were submitted for analysis. Only 2 of these 10 patients had been randomly assigned to the itraconazole group in the first phase of the trial. The isolates from both these patients were susceptible to itraconazole, and both had a response to treatment. Two of the patients from whom isolates were obtained did not receive itraconazole in either phase. Isolates were available from six patients who had not had a response to placebo and who participated in the open-label phase. Isolates from three of these six patients were susceptible to itraconazole (one had two isolates obtained at different times, and both were susceptible), and all three had a response during the open-label phase. The isolates from the other three were tolerant in two cases and resistant in one, and none of the three had a response ( $P=0.018$  for the comparison with patients with susceptible isolates when both phases of the study were considered;  $P=0.1$  for the comparison only in the open-label phase).

#### DISCUSSION

The results of this double-blind, randomized, placebo-controlled study indicate that patients with corticosteroid-dependent allergic bronchopulmonary aspergillosis generally benefit from concurrent itraconazole therapy. Improvements were noted in association with itraconazole therapy for most components of the response criteria, including the immunologic and physiologic criteria and the corticosteroid dose, but not in the absence of radiographic infiltrates related to allergic bronchopulmonary aspergillosis. Whereas the lack of a significant effect on pulmonary infiltrates might suggest that acute exacerbations of this condition are not diminished by itraconazole, the brevity of the double-blind phase might also explain this result. Moreover, only one fifth of patients who could be evaluated (and an even smaller fraction of patients in the open-label phase) were not considered to have had a response with respect to this component, which was the lowest rate of nonresponse in any of the categories. Therefore, the high rate of response in this component could be a confounder.

Several limitations of the study should be considered. The proportion of men was significantly smaller in the itraconazole group than in the placebo group. This discrepancy might have caused a trend favorable to placebo, since the response rate associated with itraconazole was greater in men. However, the treatment effect remained after adjustment for sex. In addition, serum itraconazole concentrations were not routinely monitored. Some patients do not absorb itraconazole well, usually as a result of hypochlorhydria or intestinal abnormalities, and others have low serum concentrations as a result of drug interactions<sup>38</sup> (although known antagonistic drugs were proscribed). Therefore, if serum concentration had been moni-

tored as a means of indicating the need for dose adjustments, the response associated with itraconazole might have been greater.

The rate of response to itraconazole in both phases was close to that predicted from previous uncontrolled studies.<sup>24-26</sup> That the response in patients receiving placebo was considerably greater than predicted may reflect a previously described variability in the course of allergic bronchopulmonary aspergillosis or the lack of a placebo preparatory period (common in trials of asthma therapy to ensure that patients are receiving the lowest dose of concurrent medication before randomization). It may also reflect a psychological influence on the course of disease in some patients participating in a study involving a new medication. Our results may indicate that some patients with allergic bronchopulmonary aspergillosis are receiving higher maintenance doses of corticosteroids than they require, at least over the short term. The data gathered on this so-called placebo effect should be useful in the planning of future trials.

The presumed mechanism of the significantly greater response in the itraconazole group than in the placebo group is the drug's antifungal activity. Itraconazole may reduce the colonization of aspergillus in the airways and its proliferation in airway mucus. This effect is analogous to the effect of itraconazole described in patients with invasive aspergillosis.<sup>33,39,40</sup> It cannot be determined with certainty whether an isolate obtained from sputum culture is related to a patient's ongoing allergic bronchopulmonary aspergillosis. However, the correlation of susceptibility-test results with *in vivo* results suggests that the responses may be related to an antimicrobial effect of the drug. In addition, it is possible that only patients with a susceptible isolate will have a response.

It also is possible that itraconazole has an antiinflammatory effect. Itraconazole can increase the serum concentrations of methylprednisolone, apparently by interfering with hepatic enzymes that metabolize both drugs.<sup>41-43</sup> However, only two patients assigned to itraconazole treatment were receiving methylprednisolone, and the drug interaction described does not apply to prednisone,<sup>42,43</sup> the corticosteroid used by all the other patients enrolled in the trial.

The beneficial effect of itraconazole appeared to be achieved without associated toxic effects. This finding is consistent with the paucity of adverse effects observed in a previous, large study.<sup>44</sup> The only exception involved the vitality subscale of the SF-36, for which scores improved less in the itraconazole group than in the placebo group during the double-blind phase. This finding may suggest that a subjective sense of fatigue was associated with the use of itraconazole during the double-blind phase and with reversal of fatigue during the open-label phase, when the dose was halved. However, the meaning of this finding is unclear, since there were differences between the itra-

conazole and placebo groups with respect to changes in the score on the vitality subscale but no differences in the absolute scores, and since there were no significant differences between the groups in scores on the eight other subscales in either phase of the trial. Moreover, there was no disparity between the two groups in recorded adverse effects that could be associated with an alteration in the subjective sense of vitality.

The results of the open-label study — particularly for patients who had received placebo during the double-blind phase — suggest that low doses of itraconazole may be equally beneficial and that the lower itraconazole dose may also be useful as maintenance therapy to sustain remissions. The 40 percent rate of response in the open-label phase among patients who had previously received placebo is especially noteworthy, since patients who had a response to placebo in the double-blind phase were, by definition, not included in the calculation of that rate; thus, the rate occurred in a group not highly likely to have been responsive to placebo. The 31 percent rate of response among patients who had not had a response to itraconazole during the double-blind phase may indicate that some patients required a longer course of therapy before a response occurred and suggests that a response rate of approximately 75 percent may be attained with 32 weeks of therapy. However, the fact that fewer patients in the itraconazole group than in the placebo group had not had a response during the double-blind phase meant that there were fewer such patients in the open-label phase. Thus, we cannot firmly conclude that this 31 percent rate of response differs from the 19 percent rate of response to placebo during the double-blind phase.

Although our results substantiate the tentative conclusions of previous, uncontrolled trials that itraconazole may be beneficial in the treatment of allergic bronchopulmonary aspergillosis, the optimal duration of therapy has not been defined. In addition, it is unclear whether itraconazole would be beneficial for all stages of the disease. Since no patients with cystic fibrosis were enrolled in the study, the possible benefits of treatment in this population are uncertain, although patients with cystic fibrosis were among those with a response to itraconazole in uncontrolled trials.<sup>24-27</sup> Finally, the possible benefit of itraconazole therapy for patients whose illness would not meet the entry criteria for our study, including those with a partial or related form of the disease, remains to be defined.

In conclusion, our results indicate the potential efficacy of an antimicrobial agent in the treatment of an allergic disease. Additional randomized, controlled studies of treatment for allergic bronchopulmonary aspergillosis are needed.

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