[Original Research]

CHEST

A Randomized Trial of Itraconazole vs Prednisolone in Acute-Stage Allergic Bronchopulmonary Aspergillosis Complicating Asthma

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OBJECTIVE: Whether itraconazole monotherapy is effective in the acute stage of allergic bronchopulmonary aspergillosis (ABPA) remains unknown. The goal of this study was to compare the efficacy and safety of itraconazole and prednisolone monotherapy in ABPA.

METHODS: Treatment-naive subjects with ABPA complicating asthma (January 2012 to December 2013) were randomized to receive either oral itraconazole or prednisolone for 4 months. The study was not blinded. The primary outcomes were proportion of subjects exhibiting a composite response after 6 weeks, percent decline in IgE after treatment, and numbers of subjects experiencing exacerbation. The secondary outcomes included the time to first exacerbation, change in lung function, and treatment-related adverse effects.

RESULTS: A total of 131 subjects (prednisolone group, n = 63; itraconazole group, n = 68) were included in the study. The number of subjects exhibiting a composite response was significantly higher in the prednisolone group compared with the itraconazole group (100% vs 88%; $P = .007$). The percent decline in IgE after 6 weeks and 3 months and the number of subjects with exacerbations after 1 and 2 years of treatment were similar in the two groups. The time to first exacerbation (mean: 437 vs 442 days) and the improvement in lung function after 6 weeks was also similar in the two groups. The occurrence of side effects was significantly higher in the glucocorticoid arm ($P < .001$).

CONCLUSIONS: Prednisolone was more effective in inducing response than itraconazole in acute-stage ABPA. However, itraconazole was also effective in a considerable number and, with fewer side effects compared with prednisolone, remains an attractive alternative in the initial treatment of ABPA.

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KEY WORDS: allergic bronchopulmonary aspergillosis; allergic bronchopulmonary mycosis; antifungal agents; aspergillus; azoles; bronchiectasis; cystic fibrosis; voriconazole

ABBREVIATIONS: ABPA = allergic bronchopulmonary aspergillosis; HRCT = high-resolution CT

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Allergic bronchopulmonary aspergillosis (ABPA) is a complex pulmonary disorder caused by immunologic reactions mediated against *Aspergillus fumigatus*.[1,2] One of the most prevalent of the *Aspergillus*-related disorders,[3] the global burden of ABPA complicating asthma has been estimated at about 5 million subjects, with 1.4 million cases in India alone.[4,5] The most common clinical presentation of ABPA is with poorly controlled asthma[6]; other common manifestations include fever, hemoptysis, and recurrent pulmonary infiltrates. The condition is treatment responsive, and early diagnosis and treatment can prevent progression to end-stage fibrosis.[7] Otherwise, the inflammatory process can be relentless, culminating in bronchiectasis and pulmonary fibrosis.

ABPA is currently classified into seven stages.[8] When the patient is diagnosed for the first time, the disease is classified as the acute stage (stage 0 or 1). Stages 2 to 5 are defined in patients undergoing treatment, and stage 6 is advanced ABPA with pulmonary hypertension and/or respiratory failure.[9] Oral glucocorticoids are currently the preferred agents in the management of acute-stage ABPA.[8,10] However, their benefits are offset by unacceptable side effects, including weight gain, osteopenia, acne, diabetes mellitus, and growth retardation in children. An alternate treatment approach in ABPA is the use of antifungal azoles.[11] These agents act by decreasing the fungal burden, thereby reducing the antigenic stimulus for the ongoing inflammatory activity.[12] Previously, studies have used itraconazole, primarily as a steroid-sparing agent, with an efficacy of approximately 60%.[13,14] Itraconazole, however, is also widely recommended as a first-line drug in the treatment of ABPA,[15,16] despite the fact that there are no randomized trials of azole monotherapy in acute-stage ABPA.

We hypothesized that glucocorticoids would be superior to itraconazole in the initial treatment of patients with ABPA. The present article reports the outcomes of a randomized trial comparing itraconazole and glucocorticoid monotherapy in subjects with acute-stage ABPA complicating asthma.

Materials and Methods

This open-label, single-center, randomized controlled trial was conducted in the Chest Clinic of PGIMER, Chandigarh. The subjects were enrolled between January 2012 and December 2013, and scheduled for follow-up for at least 2 years. The study protocol was approved by the Ethics Review Committee (MS/1398/Res/1838), and written informed consent was obtained from all study subjects.

Study Subjects

Subjects were included in the study if they fulfilled the criteria for ABPA defined by presence of all of the following: (1) asthma; (2) immediate cutaneous hyperreactivity on *Aspergillus* skin test or serum *A fumigatus*-specific IgE $>$ 0.35 kUA/L; and (3) elevated serum total IgE $>$ 1,000 IU/mL. In addition, subjects had to have two of the following features: (1) presence of precipitating antibodies against *A fumigatus* in serum; (2) fixed or transient radiographic pulmonary opacities; (3) peripheral blood eosinophil count $>$ 1,000 cells/μL; and (4) bronchiectasis on high-resolution CT (HRCT) scanning of the thorax.[17] Subjects with any of the following were excluded: (1) intake of systemic glucocorticoids or antifungal azoles for $\geq$ 3 weeks in the last 12 months; (2) subjects with a diagnosis of cystic fibrosis, aspergillomas, chronic pulmonary aspergillosis, invasive pulmonary aspergillosis, respiratory infection aggravating asthma, or ABPA; (3) immunosuppressive conditions such as uncontrolled diabetes mellitus, chronic renal failure, and chronic liver disease; (4) immunosuppressive therapy; (5) omalizumab therapy; (6) pregnancy; (7) enrollment in another trial of ABPA; and (8) failure to provide informed consent. An *Aspergillus* skin test, serum IgE (total and *A fumigatus*-specific), *Aspergillus* precipitins, total eosinophil count, spirometry, chest radiograph, and HRCT chest imaging were performed in all subjects, as previously described.[18] CT chest scan was used to classify ABPA as serologic ABPA, ABPA with bronchiectasis, and ABPA with high-attenuation mucus.[19]

Randomization

Subjects meeting the inclusion criteria were randomized 1:1 to either the itraconazole or the glucocorticoid group (Fig 1). The randomization sequence was computer generated, and the assignments were placed in opaque sealed envelopes. The assignment of a patient to a group was made sequentially.

Study Procedure

Subjects received one of the following treatments. The itraconazole group received oral itraconazole capsules (Fungitrace, Lifecare Innovations) 200 mg twice daily along with meals (or orange juice) for 4 months. Drug levels of itraconazole were not performed and during the study period, gastric acid-reducing medications were not allowed. The prednisolone group received oral prednisolone (Omnacortil, Macleod's Pharmaceuticals) 0.5 mg/kg per day for 4 weeks, 0.25 mg/kg per day for 4 weeks then 0.125 mg/kg per day for 4 weeks. Subsequently, prednisolone was tapered by 5 mg every 2 weeks and discontinued. The total duration of glucocorticoid therapy was 4 months.

Adherence to treatment was assessed by instructing the patient to bring empty pill covers of the drug to outpatient visits. For the control of asthma, treatment with inhaled corticosteroids, long-acting β_2-agonists (formoterol), and leukotriene receptor antagonists was allowed in both groups, at the discretion of the treating physician.

We monitored the subjects with history and physical examination, chest radiograph, and serum IgE levels (total) every 6 weeks for 6 months and then every 6 months or earlier if there was worsening in symptoms. Spirometry was repeated at the second visit. The subjects were clinically monitored for adverse reactions such as cataracts, glaucoma, and weight gain. Fasting plasma glucose, BP, and liver function tests were also measured every 6 weeks.

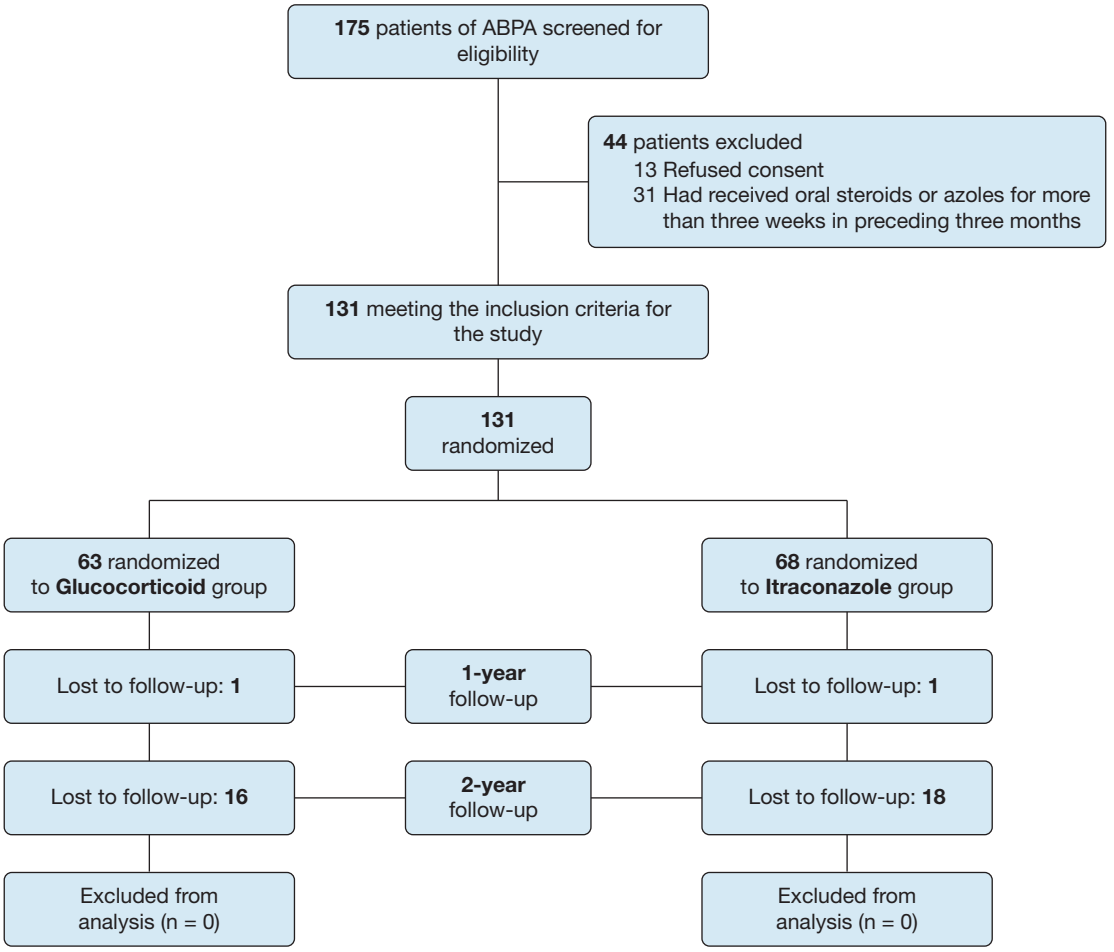

Figure 1 – *CONSORT diagram demonstrating the flow of participants in the study. ABPA = allergic bronchopulmonary aspergillosis.*

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End Points

Clinical improvement in cough and dyspnea was documented on a four-point scale, described previously,[10] as follows: 1, no improvement or worsening; 2, mild improvement (up to 25% reduction from baseline); 3, moderate improvement (25%-75% reduction from baseline); and 4, significant improvement (>75% reduction from baseline). We classified treatment effects as: (1) composite response—defined after 6 weeks of treatment, based on improvement in cough and dyspnea (> 75% of baseline) accompanied by a partial (≥ 50%)/total clearance of chest radiographic lesions (if present prior to treatment initiation), and decline in serum total IgE by ≥ 25%; and (2) incidence of ABPA exacerbation—clinical and/or radiologic worsening along with doubling of the serum total IgE over the previous baseline value. All subjects experiencing exacerbations were investigated with chest radiograph, total IgE, sputum for acid-fast bacilli and culture for bacterial pathogens. The first ABPA exacerbation was treated with oral prednisolone at a dosage of 0.5 mg/kg per day for 4 weeks, then 0.25 mg/kg per day for 4 weeks, followed by 0.125 mg/kg per day for 4 weeks, then decreased by 5 mg/week for a total of 4 months. All subsequent ABPA exacerbations were treated with prednisolone at the aforementioned dosage along with itraconazole 400 mg/d for 6 months. Changes in patients with only clinical worsening (no radiologic worsening or doubling of serum total IgE) were attributed to asthma exacerbation.

The primary outcomes were as follows: (1) proportion of subjects exhibiting a composite response to treatment after 6 weeks; (2) percent decline in total IgE (baseline IgE minus time point IgE/baseline IgE) after 6 weeks and 3 months; (3) complete remission after 3 and 6 months of stopping treatment; and (4) numbers of subjects experiencing an exacerbation 1 year and 2 years after treatment. The secondary outcomes were as follows: (1) time to first ABPA exacerbation; (2) change in lung function (FEV_1 and FVC) after 6 weeks; (3) number of asthma and ABPA exacerbations; and (4) treatment-related adverse effects.

Sample Size

We assumed the efficacy of itraconazole to be approximately 80% in glucocorticoid-naive subjects with acute-stage ABPA, whereas the effectiveness of daily-dose prednisolone is about 100% in our clinical experience. Assuming a difference in the primary outcome measure of 99% in the glucocorticoid group and 80% in the itraconazole group, 100 subjects are required for the study to have a 90% power of detecting significance at the 5% level. With a dropout rate of 30%, the sample size comes out to be 130 subjects.

Statistical Analysis

Data were analyzed by using SPSS version 22.0 (IBM Corporation) and are expressed as number with percentage or mean ± SD or 95% CIs. The differences between categorical and continuous variables were analyzed by using the χ^2 test (or the Fisher exact test) and the Mann-Whitney *U* test (or Student *t* test), respectively. An intention-to-treat analysis was performed. The effect of missing data was

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further explored by using multiple imputation and worst-case scenario analysis. A one-way ANCOVA was performed to compare the response at 6 weeks in the two groups while controlling for baseline total IgE and FEV_1. Decline in IgE was analyzed by using multifactorial repeated measures ANOVA, with Bonferroni adjustment for multiple comparisons; the within-group factor was time (baseline, 6 weeks, and 3 months), and the between-group factor was the treatment groups. Survival curves were constructed to study the effect of treatment on the time to first exacerbation by using Kaplan-Meier analysis, and the group differences were analyzed by using the log-rank test. Statistical significance was assumed at a P value $< .05$.

Results

Of the 175 subjects screened, 44 were excluded before randomization (Fig 1). A total of 131 subjects with ABPA were randomized to either the prednisolone (n = 63) or the itraconazole (n = 68) group. None had received azole or glucocorticoids for > 3 weeks in the previous year, and all were being managed as having asthma. The subject withdrawal rate was similar in the two groups at 1 year (two subjects, one in each group) and 2 years (glucocorticoids: 16 of 63 [25.4%]; itraconazole: 18 of 68 [26.5%]). The baseline characteristics were similar in the two groups (Table 1). The mean ± SD age of the study subjects (53% male) was 37 ± 13.9 years. The mean duration of asthma at the time of diagnosis was 12.3 years. The FEV_1 was < 60% in approximately 43%, and the majority (93%) had bronchiectasis on HRCT chest imaging. High-attenuation mucus was observed in 40.5% of subjects. The serum IgE (total and *A fumigatus*-specific) and eosinophil counts were similar in the two groups. All subjects were receiving asthma treatment with inhaled corticosteroids and long-acting β_2-agonists, and 48% of the subjects were also receiving leukotriene receptor antagonists. The dose of inhaled corticosteroids was similar in the two groups. The mean duration of follow-up of the study population was 88.9 ± 43.6 months; however, all analyses have been performed until 2 years of follow-up.

Primary Outcomes

The proportion of subjects exhibiting a composite response to treatment at 6 weeks was significantly higher in the prednisolone group vs the itraconazole group (63 [100%] vs 60 [88%]; $P = .007$). Even after adjusting for baseline total IgE ($F = 0.573$; $P = .45$) or FEV_1 ($F = 0.183$; $P = .67$), the difference in composite response remained statistically significant (ANCOVA, $P = .001$). The percent decline in IgE was similar in the two groups at 6 weeks (55% vs 52%; $P = .87$) and 3 months (67% vs 66%; $P = .80$) (Fig 2). For other outcomes, the eight subjects who did not respond to itraconazole were excluded because they subsequently received prednisolone for disease activity control. The number of subjects with complete remission after 3 and 6 months of stopping treatment were similar in the two groups. Overall, 13 (10.6%) and 31 (25.2%) subjects experienced an exacerbation, after 1 and 2 years, respectively, of completing treatment. The numbers of subjects with exacerbations after 1 and 2 years were similar in the two groups (Table 2). There was no difference in exacerbation rate at 1 and 2 years even following multiple imputation and worst-case scenario analysis (e-Table 1). There was good response of the exacerbations with treatment, and only 12 of the 31 subjects experienced recurrent (≥ 2) exacerbations.

Secondary Outcomes

The mean time to first exacerbation (prednisolone vs itraconazole: 437 vs 442 days) was similar in the two groups (Fig 3). The change in lung function (both FEV_1 and FVC) on spirometry at 6 weeks was similar in the two groups (Table 2). The total number of asthma and ABPA exacerbations was similar in the two groups. The occurrence of adverse events, including cushingoid habitus, weight gain, acne, and hypertrichosis, was significantly higher in the glucocorticoid arm (Table 3). Liver function test abnormalities were observed in nine (15%) subjects in the itraconazole group. These abnormalities were transient, however, and none led to discontinuation of the study drug. No study subject in the itraconazole group developed cushingoid features. There was no instance of pulmonary TB or non-tuberculous mycobacterial infection in any subject during the study.

The clinical characteristics of the eight subjects in the itraconazole group who did not exhibit a composite response at 6 weeks are shown in e-Table 2. We could not identify any predictor associated with failure to respond to itraconazole (Table 4). All eight subjects were treated with prednisolone, and they exhibited a composite response after 6 weeks of treatment. Six of these eight subjects experienced an exacerbation of ABPA, and four experienced recurrent ABPA exacerbations during follow-up.

Discussion

The results of this study suggest that oral glucocorticoids were more effective than itraconazole (100% vs 88%) in

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TABLE 1] Baseline Characteristics of the Study Population

Characteristic	Prednisolone Group (n = 63)	Itraconazole Group (n = 68)	Total (N = 131)	*P* Value
Demographic variables				
Age, y	36.6 ± 13.5	37.4 ± 14.5	37.0 ± 13.9	.89
Male sex	29 (46)	41 (60.3)	70 (53.4)	.10
Height, cm	162.8 ± 9.5	165.5 ± 10.5	164.1 ± 10.1	.10
Weight, kg	54.2 ± 12.9	58.9 ± 15.2	56.6 ± 14.3	.07
Duration of asthma, y	12.7 ± 9.6	11.9 ± 9.1	12.3 ± 9.3	.63
Hemoptysis	22 (34.9)	19 (27.9)	41 (31.3)	.39
Brownish-black mucus plugs	11 (17.5)	19 (27.9)	30 (22.9)	.15
Spirometry				
FEV_1, L	1.8 ± 0.83	2.1 ± 0.93	1.9 ± 0.89	.07
FVC, L	2.6 ± 0.9	2.9 ± 1.0	2.8 ± 0.97	.07
FEV_1/FVC	65.2 ± 13.4	69.3 ± 14.1	67.3 ± 13.8	.10
Severity of obstruction				
Normal ($FEV_1 > 80\%$)	15 (24.2)	19 (30.6)	34 (27.4)	.72
Mild obstruction (FEV_1 60%-80%)	20 (32.3)	22 (35.5)	42 (33.9)	…
Moderate obstruction (FEV_1 40%-60%)	15 (24.2)	12 (19.4)	27 (21.8)	…
Severe obstruction ($FEV_1 < 40\%$)	13 (20.6)	15 (22.1)	28 (21.4)	…
Chest radiograph findings				
Abnormal chest radiograph	54 (85.7)	56 (82.4)	110 (84.0)	.60
Fleeting opacities	40 (63.5)	46 (67.6)	86 (65.6)	.62
CT chest scan findings				
Normal HRCT scan (Serologic ABPA)	5 (7.9)	4 (5.9)	9 (6.9)	.64
Bronchiectasis	58 (92.1)	64 (94.1)	122 (93.1)	.64
High-attenuation mucus	22 (34.9)	31 (45.6)	53 (40.5)	.21
No. of segments involved by bronchiectasis	7.7 (4.9)	7.4 (5.2)	7.5 (5.0)	.79
Immunologic findings				
Aspergillus skin test	59 (93.7)	65 (95.6)	124 (94.7)	.62
A fumigatus-specific IgE levels, kUA/L	33.4 ± 26.7	29.4 ± 21.8	31.3 ± 24.3	.66
Total IgE levels, IU/mL	11,338 ± 11,953	9,800 ± 8,686	10,540 ± 10,374	.70
Total eosinophil count, cells/μL	1,549 ± 2,321	1,014 ± 976	1,271 ± 1,770	.50
Aspergillus precipitins	31 (49.2)	35 (51.5)	66 (50.4)	.80
Asthma treatment				
Subjects taking ICS	63 (100)	68 (100)	131 (100)	.99
Dose of ICS (BDPE), μg	383 ± 259	392 ± 254	388 ± 256	.84
Subjects taking LABA	63 (100)	68 (100)	131 (100)	.99
Dose of formoterol, μg	14.1 ± 6.2	13.9 ± 6.5	14 ± 6.3	.89
Subjects taking LTRAs	30 (47.6)	33 (48.5)	63 (48.1)	.92

Data are presented as mean ± SD or No. (%). ABPA = allergic bronchopulmonary aspergillosis; BDPE = beclomethasone dipropionate equivalent; HRCT = high-resolution CT; ICS = inhaled corticosteroid; LABA = long-acting β-agonist; LTRAs = leukotriene receptor antagonists.

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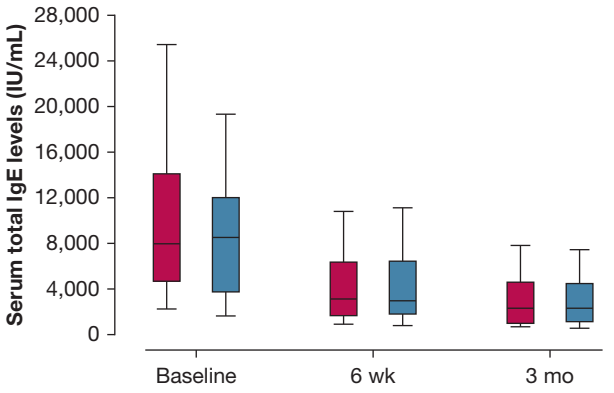

Figure 2 – *Box and whisker plots showing the IgE levels at baseline, 6 weeks, and 3 months in the two groups (prednisolone: red plots; itraconazole: blue plots). Box plots represent the 25th and 75th percentiles, with the internal horizontal lines showing the median and T bars showing the 10th and 90th percentiles. There was significant decline in IgE from baseline to 6 weeks and 3 months (P = .0001); however, the decline was not significantly different between the two groups either at 6 weeks (P = .262) or 3 months (P = .595).*

producing treatment response in patients with acute-stage ABPA complicating asthma. However, the time to first exacerbation and the number of subjects experiencing exacerbation were similar in the two groups (after excluding subjects not exhibiting an initial response to itraconazole). Importantly, the occurrence of adverse reactions was significantly higher in the glucocorticoid arm. The present study used slightly different criteria for diagnosis (eosinophil count of 1,000 cells/μL rather than 500 cells/μL) and assessing treatment responses (response assessed at 6 weeks rather than 8 weeks; exacerbation defined as doubling of serum total IgE rather than 50% increment in IgE) than those proposed by the International Society for Human and Animal Mycology ABPA working group[20] because the present study was planned before those guidelines.

The ideal design for the present study would have been three groups (glucocorticoid monotherapy, itraconazole monotherapy, and a combination of itraconazole plus

TABLE 2] Outcomes of Study Subjects Treated With Prednisolone or Itraconazole (N = 131)

Outcome	Prednisolone Group (n = 63)	Itraconazole Group (n = 68)	Estimated Difference (95% CI)	*P* Value
Primary outcomes				
Subjects with response following 6 wk of treatment[a]	63 (100%)	60 (88.2%)	−11.8 (−21.5 to −3.7)	.007
Subjects with response following 3 mo of treatment	63 (100%)	60 (100%)	0 (−0.06 to 0.06)	…
Complete remission following 3 mo of stopping treatment	60 (95.2%)	59 (98.3%)	−0.03 (−0.05 to 0.12)	.39
Complete remission following 6 mo of stopping treatment	58 (92.1%)	59 (98.3%)	0.05 (−0.05 to 0.14)	.13
Percentage decline in IgE following 6 wk of treatment (n = 123)	54.5 (48.9-60.1)	51.8 (42.9-60.8)	−2.7 (−7.6 to 13.4)	.87
Percentage decline in IgE following 3 mo of treatment (n = 123)	66.9 (62.0-71.8)	65.6 (59.1-72.1)	−1.3 (−6.7 to 9.3)	.80
No. of subjects experiencing exacerbation following 1 y of treatment (n = 123)	6 (9.5%)	7 (11.7%)	−2.1 (−13.8 to 9.2)	.93
No. of subjects experiencing exacerbation following 2 y of treatment (n = 123)	14 (22.2%)	17 (28.3%)	−6.1 (−21.3 to 9.2)	.44
Secondary outcomes				
Time to first exacerbation (n = 123)	437 (307-567)	442 (369-521)	8 (−76 to 61)	.91
Difference in FEV_1 following 6 wk of treatment (n = 123)	0.33 (0.26-0.41)	0.30 (0.22-0.37)	0.03 (−0.07 to 0.13)	.20
Difference in FVC following 6 wk of treatment (n = 123)	0.37 (0.19-0.54)	0.37 (0.26-0.49)	0.08 (−0.06 to 0.22)	.42
Subjects with exacerbation following 6 mo of treatment	6 (9.5%)	6 (10.0%)	0.01 (−0.11 to 0.12)	.93
Total No. of ABPA exacerbations	0.57 (0.32-0.82)	0.83 (0.48-1.18)	−0.26 (−0.69 to 0.17)	.32
Total No. of asthma exacerbations	0.48 (0.28-0.67)	0.62 (0.36-0.87)	−0.14 (−0.46 to 0.18)	.45

Data are presented as mean (95% CI), unless otherwise stated.
[a]All other outcomes have been analyzed following exclusion of the eight subjects who failed to exhibit a response after 6 weeks of treatment.

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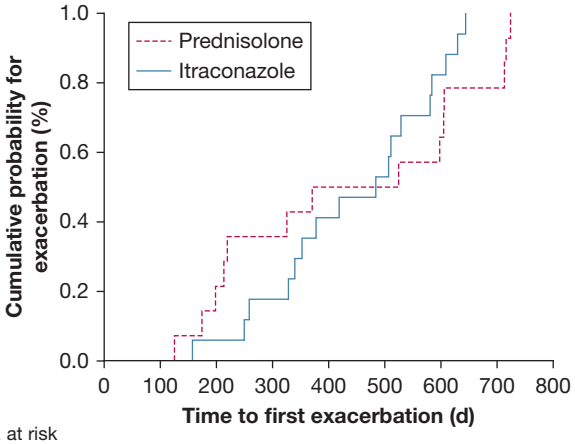

No. at risk									
Prednisolone	14	14	11	9	7	7	5	3	0
Itraconazole	17	17	16	14	10	8	3	0	0
No. on follow-up									
Prednisolone	63	63	63	63	59	50	48	47	43
Itraconazole	60	60	59	59	58	55	53	50	47

Figure 3 – *Time to first exacerbation in subjects receiving itraconazole (solid line) vs prednisolone (dotted line) in 123 subjects with ABPA (eight subjects failing initial treatment were excluded). The time to first exacerbation in this group was similar in the two groups. The number at risk in each group denotes the numbers of patients still at risk of experiencing the first exacerbation. See Figure 1 legend for expansion of abbreviation.*

glucocorticoids). However, the study question was the efficacy of itraconazole monotherapy in acute-stage ABPA, the potential advantage being that it will eliminate the exposure to glucocorticoids altogether, and its ensuing side effects.[20] Itraconazole has also been reported to have several side effects, including serious adverse reactions such as neuropathy and liver dysfunction.[21-23] Although we recorded transaminitis in 15% of the subjects taking itraconazole, none of the study subjects discontinued treatment. Other side effects were probably not seen because itraconazole was used for only 4 months, unlike previous studies in which it was used for longer durations.[24] An important concern with azole therapy is the emerging risk of azole-resistant *Aspergillus* species.[25,26] Hence, treatment with itraconazole should be short courses (4-6 months) rather than prolonged or indefinite therapy.[12] Other problems with itraconazole include its interaction with glucocorticoids, both inhaled (budesonide and fluticasone) and oral (methylprednisolone), with the potential for iatrogenic Cushing's syndrome.[27,28]

What are the clinical implications of this study? Glucocorticoids were more effective than itraconazole monotherapy in acute-stage ABPA, with a number-needed-to-treat to prevent one treatment failure being nine (95% CI, 5-18). This finding is not surprising because glucocorticoids, by their potent anti-inflammatory action, bring about significant control of the immunologic activity. Despite a lower success rate, itraconazole was still effective in approximately 88% of patients with ABPA. In fact, the course of patients who did not fail initial treatment with itraconazole was similar to those taking glucocorticoids. Moreover, itraconazole therapy was associated with minimal adverse events compared with glucocorticoids. Thus, the balance of safety and efficacy indicates that itraconazole is an alternate option in acute-stage ABPA, especially in those in whom a glucocorticoid-sparing agent is required (eg, patients with uncontrolled diabetes mellitus, severe osteoporosis, obesity). Itraconazole is likely to be even more effective in real-world situations because the patients in the present study were those with

TABLE 3] Adverse Reactions Noted in Study Subjects Treated With Prednisolone or Itraconazole (n = 123)

Adverse Reaction	Prednisolone Group (n = 63)	Itraconazole Group (n = 60)[a]	Estimated Difference (95% CI)	*P* Value
Discontinuation of study drug	0	0	…	…
Cushingoid habitus	52 (82.5%)	0	82.5 (69.9 to 89.9)	.0001
Hypertension	0	0	…	…
Hyperglycemia	2 (3.2%)	0	3.2 (−3.3 to 10.9)	.50
Hypertrichosis	12 (19.1%)	0	19.1 (9.2 to 30.4)	.002
Acne	11 (17.5%)	0	17.5 (7.9 to 28.6)	.002
Striae	8 (12.7%)	0	12.7 (4.1 to 23.1)	.003
Weight gain (> 10% of baseline) at 6 wk	37 (58.7%)	2 (3.3%)	55.4 (40.7 to 66.9)	.0001
Mood changes	3 (4.8%)	0	4.8 (−2.0 to 13.1)	.24
Fatigue	3 (4.8%)	8 (13.3%)	−8.6 (−19.9 to 1.9)	.26
Liver function test abnormalities	0	9 (15%)	−15 (−26.1 to −6.0)	.001
Nausea	0	2 (3.3%)	−3.3 (−11.4 to 2.9)	.24

[a]The outcomes have been analyzed following exclusion of the eight subjects who failed to exhibit a response after 6 weeks of treatment.

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TABLE 4] Baseline Characteristics of Patients in the Itraconazole Group Who Did Not Exhibit a Response at 6 Weeks

Characteristic	Responders (n = 60)	Nonresponders (n = 8)	*P* Value
Demographic variables			
Age, y	38.3 (34.7-41.9)	30.5 (15.8-45.2)	.10
Male sex	35 (58.3%)	6 (75%)	.46
Duration of asthma, y	12.5 (9.9-15.0)	7.3 (1.7-12.9)	.13
Spirometry			
FEV_1, L	2.1 (1.9-2.3)	1.9 (1.2-2.7)	.63
FVC, L	2.9 (2.7-3.2)	2.6 (1.7-3.5)	.27
FEV_1/FVC	68.6 (64.9-72.3)	74.3 (65.3-83.3)	.30
Chest radiograph findings			
Abnormal chest radiograph	50 (83.3%)	6 (75%)	.62
Fleeting opacities	43 (71.7%)	3 (37.5%)	.10
HRCT chest findings			
Bronchiectasis	56 (93.3%)	8 (100%)	.99
No. of segments involved	7.2 (5.2-8.6)	9 (5.9-12.1)	.22
High-attenuation mucus	28 (46.7%)	3 (37.5%)	.72
Immunological findings			
A fumigatus-specific IgE levels, kUA/L	29.9 (24.3-35.5)	25.3 (6.4-44.1)	.47
Total IgE levels, IU/mL	10,168 (7,844-12,492)	7,039 (2,458-11,619)	.38
Total eosinophil count, cells/μL	1,068 (805-1,332)	604 (296-911)	.25

Data are presented as mean (95% CIs), unless otherwise stated. See Table 1 legend for expansion of abbreviation.

a particularly severe form of ABPA and are not necessarily representative of ABPA in other countries. The only caution is that the initial treatment must be carefully monitored. Ideally, therapeutic drug monitoring should be performed in the initial 4 weeks, especially in those who do not respond, and failure to improve by 6 weeks should prompt consideration of alternative therapy, especially glucocorticoids. Unfortunately, the present study could not identify any predictor of failure to response to itraconazole, which could have helped in avoiding itraconazole in a specific subgroup (Table 4).

The present study has a few limitations. It was conducted at a single center and was not blinded, thus introducing a potential of selection bias. Also, a subjective scoring was kept for clinical improvement, although we did try to overcome this limitation by corroborating the clinical and radiologic improvement with an objective marker (total serum IgE levels). Therapeutic drug monitoring for itraconazole could not be performed due to nonavailability and is a major limitation. The lack of drug monitoring precludes the ability to exclude low steady-state levels as the cause of the eight itraconazole treatment failures. In addition, drug monitoring would have been a superior method to assess adherence. Adherence to treatment was assessed by instructing the patient to bring the empty pill covers of the drug to every outpatient visit. To enhance drug bioavailability, patients were instructed to consume itraconazole immediately following meals, and all medications reducing gastric acidity were avoided. The study did not measure the quality of life scores; however, patient-centric outcomes were scored on a semi-quantitative Likert scale. Also, the results are mainly applicable to ABPA complicating asthma. Finally, there was attrition of study participants at 2 years of follow-up, though this finding was similar in the two groups.

Conclusions

Glucocorticoids seemed to be more effective than itraconazole in acute-stage ABPA. However, itraconazole was still effective in a vast majority, with comparatively fewer side effects, and remains an attractive alternative in the initial treatment of ABPA. Approximately 12% of patients did not respond to itraconazole; hence, if itraconazole is used in acute-stage ABPA, the treatment must be closely monitored. Future studies could adopt a strategy wherein a much shorter course of glucocorticoid is used combined with itraconazole and compared with glucocorticoid alone.

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Additional information: The e-Tables can be found in the Supplemental Materials section of the online article.

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