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Early View

Original research article

A randomised trial of prednisolone *versus* prednisolone and itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma

Ritesh Agarwal, Valliappan Muthu, Inderpaul Singh Sehgal, Sahajal Dhooria, Kuruswamy Thurai Prasad, Mandeep Garg, Ashutosh Nath Aggarwal, Arunaloke Chakrabarti

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A randomized trial of prednisolone versus prednisolone and itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma

[3]Ritesh Agarwal MD, DM
[1]Valliappan Muthu MD, DM
[1]Inderpaul Singh Sehgal MD, DM
[1]Sahajal Dhooria MD, DM
[1]Kuruswamy Thurai Prasad MD, DM
[3]Mandeep Garg MD[*]
[3]Ashutosh Nath Aggarwal MD, DM
[3]Arunaloke Chakrabarti MD[§]

[1]Assistant Professor, and [3]Professor
Department of Pulmonary Medicine, Department of Radiodiagnosis and Imaging[*], Department of Medical Microbiology[§]
Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India

Address for Correspondence
Dr. Ritesh Agarwal MD, DM
Professor
Department of Pulmonary Medicine
Postgraduate Institute of Medical Education and Research (PGIMER)
Chandigarh. India. 160012
Phone: +91 172 275 6825 (Work)
Fax: +91 172 274 8215
Email: agarwal.ritesh@outlook.in

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Take-home message: Combination therapy with prednisolone-itraconazole resulted in a non-significant decline in the occurrence of ABPA exacerbations at 1-year than prednisolone monotherapy in acute-stage ABPA complicating asthma

ABSTRACT

Whether a combination of glucocorticoid and antifungal triazole is superior to glucocorticoid alone, in reducing exacerbations, in patients with allergic bronchopulmonary aspergillosis (ABPA) remains unknown. We aimed to compare the efficacy and safety of prednisolone-itraconazole combination versus prednisolone monotherapy in ABPA.

We randomized subjects with treatment-naïve acute-stage ABPA complicating asthma to receive either prednisolone alone (four months) or a combination of prednisolone and itraconazole (four and six months, respectively). The primary outcomes were exacerbation rates at 12 months and glucocorticoid-dependent ABPA within 24 months of initiating treatment. The key secondary outcomes were response rates and percentage decline in serum total IgE at six weeks, time to first ABPA exacerbation, and treatment-emergent adverse effects (AE).

We randomized 191 subjects to receive either prednisolone (n=94) or prednisolone-itraconazole combination (n=97). The one-year exacerbation rate was 33% and 20.6% in the prednisolone and the prednisolone-itraconazole arms, respectively (p=0.054). None of the participants progressed to glucocorticoid-dependent ABPA. All the subjects experienced a composite response at 6-weeks, along with a decline in serum total IgE (mean decline, 47.6% vs. 45.5%). The mean time to first ABPA exacerbation (417 days) was not different between the groups. None of the participants required modification of therapy due to AE.

There was a trend towards a decline in ABPA exacerbations at 1-year with the prednisolone-itraconazole combination than prednisolone monotherapy. A three-arm trial comparing itraconazole and prednisolone monotherapies with their combination, preferably in a multicentric design, is required to define the best treatment strategy for acute-stage ABPA.

Keywords: abpa; abpm; allergic bronchopulmonary mycosis; asthma; cystic fibrosis; aspergillus; azoles; bronchiectasis; antifungal agents

INTRODUCTION

Allergic bronchopulmonary aspergillosis (ABPA) is an allergic lung disorder caused by hypersensitivity reactions mounted against the fungus *Aspergillus fumigatus*.[1] Patients commonly manifest with poor asthma control, recurrent pulmonary opacities, and hemoptysis.[2] Interestingly, ABPA lies at an intersection of allergic and infective disorders, and both factors contribute to its pathogenesis.[3] The fungus incites profound pulmonary inflammation, and in contrast to other allergies, the inciting factor (i.e., *A.fumigatus*) is viable in the tracheobronchial tree.[4] While monotherapy with either glucocorticoids or antifungal triazoles has been found to be effective in the treatment of ABPA, a combination of both glucocorticoid and triazole has not been systematically evaluated.[5-7] We hypothesized that a combination of oral corticosteroids and antifungal azole might be more effective than corticosteroids alone in controlling disease activity and reducing the risk of future exacerbations. Herein, we report the results of a randomized trial evaluating a combination of prednisolone and itraconazole versus prednisolone alone in patients with ABPA complicating asthma.

METHODS

We conducted an investigator-initiated, parallel-group, open-label, randomized controlled trial (RCT) involving subjects with ABPA attending the Chest Clinic of this institute. The Institute Ethics Committee approved the study protocol (File S1; NK/2047/Res/521), and we obtained written consent from all the subjects before enrolment. We registered the study protocol at clinicaltrials.gov (study identifier: NCT02440009). We have reported the study results according to the consolidated standards of reporting trials (CONSORT) statement.

Inclusion criteria: We prospectively screened consecutive subjects with treatment-naïve acute-stage ABPA complicating asthma and included them if they met both the following criteria: (1) immediate cutaneous hyperreactivity on *Aspergillus* skin test or *A.fumigatus*-specific IgE levels >0.35 kUA/L; (2) elevated serum total IgE levels >1000 IU/mL; and, two of the following: (1) presence of precipitating antibodies (or IgG >27 mgA/L) against *A.fumigatus* in serum; (2) peripheral blood eosinophilia >1000/µL; (3) chest radiographic abnormalities consistent with ABPA; and, (4) bronchiectasis on computed tomography (CT) of the chest.

Exclusion criteria: We excluded subjects with any of the following: (a) intake of systemic glucocorticoids or triazoles for >3 weeks in the preceding six months; (b) concomitant use of medications, including voriconazole, inhaled amphotericin B, omalizumab, or other biological agents; (c) enrollment in another trial of ABPA; (d) uncontrolled diabetes mellitus, chronic renal failure, chronic liver failure, and immunosuppressive drugs; (e) pregnancy; and (f) failure to provide informed consent.

Interventions: The study participants received treatment as per the following protocol. Subjects in the prednisolone monotherapy arm received oral prednisolone sequentially at 0.5 mg/kg/day, 0.25 mg/kg/day, and 0.125 mg/kg/day for 4 weeks each. The drug was then tapered by 5 mg every two weeks and discontinued by the end of 4 months**.** Subjects in the prednisolone-itraconazole combination group were treated with oral itraconazole 200 mg twice daily for six months along

with oral prednisolone therapy (as in the prednisolone monotherapy arm)**.** Oral itraconazole was administered along with meals (or orange juice). We did not perform therapeutic drug monitoring. We checked for adherence to therapy by asking the patients to bring the empty pill covers. For asthma control, we allowed treatment with inhaled corticosteroids, long-acting β2 agonists (formoterol), and leukotriene receptor antagonist (montelukast) in both the groups, at the discretion of the treating physician.

Outcomes: The primary outcomes were: (a) relapse (exacerbation) rates within 12 months; and (b) progression to glucocorticoid-dependent ABPA within 24 months after treatment initiation. The secondary outcomes were: (a) proportion of subjects with a composite response (as defined below) after six weeks of treatment; (b) percentage decline in serum total IgE (baseline IgE minus IgE after six weeks/baseline IgE) at six weeks of treatment; (c) time to first ABPA exacerbation; and (d) treatment-related adverse effects (AEs).

Study procedure: Data was collected in case record forms, entered in a computerized data gathering platform (Epicollect 5; five.epicollect.net), and was validated against the record books before analysis. We collected the following information at baseline: (1) clinical details (age, sex, duration of asthma, history of hemoptysis, expectoration of brownish-black mucus plugs, and others); (2) immunological test results (serum total IgE, *A.fumigatus*-specific IgE and IgG, *A.fumigatus* precipitins, and peripheral blood eosinophil count); (3) spirometry (forced expiratory volume in the first second [FEV1] and forced vital capacity [FVC]); and (4) chest radiograph and CT chest findings. We observed the subjects every six weeks for six months and then every six months or earlier if there were worsening symptoms. We monitored the clinical status, chest radiograph, and serum total IgE levels at each follow-up. Spirometry was repeated at the second visit. We enquired into the adverse effects of treatment (cushingoid habitus, weight gain, hyperglycemia, striae, acne, emotional lability, depression, and liver function test abnormalities)

for the entire treatment duration. The hospital data safety and monitoring board reviewed the trial for safety on an ongoing basis.

We performed serum total IgE, *A.fumigatus*-IgE, and IgG using the commercially fluorescent enzyme immunoassay (Phadia 100, Thermo Fisher Scientific, Uppsala, Sweden), as previously described.[8] Serum precipitins were performed using the Ouchterlony double-gel diffusion method.[9, 10]

Definitions: We documented clinical improvement in cough and dyspnea on a four-point Likert scale as 1: no improvement or worsening; 2: mild improvement (up to 25% of baseline); 3: moderate improvement (25%-75% of baseline); 4: significant improvement (>75% of baseline). We classified treatment effects as: (a) composite response: defined as an improvement in cough and dyspnea (>75% of baseline) or partial (≥50%)/total clearance of chest radiographic lesions (if present before treatment) and decline in serum total IgE values by >25% after six weeks of treatment; (b) ABPA relapse (exacerbation): doubling of the baseline IgE levels irrespective of the patient's symptoms or imaging findings; or clinical or radiological worsening with 50% increase in IgE over the previous baseline value; (c) glucocorticoid-dependent ABPA: if the patient has relapsed on two or more consecutive occasions within six months of stopping treatment or requires oral glucocorticoids for asthma control; (d) asthma exacerbation: worsening of cough or dyspnea in the absence of immunological or radiological deterioration of ABPA.

Treatment of asthma, asthma exacerbations, and ABPA relapses (exacerbations) during follow-up: After initial randomization and completion of the treatment as per the trial allocation, we managed the patients as described below. We treated the first ABPA exacerbation with oral prednisolone at the doses mentioned above. The subsequent exacerbations were managed with a combination of oral prednisolone and itraconazole at doses mentioned earlier. We used voriconazole in subjects intolerant to itraconazole. We used inhaled formoterol/fluticasone (6/125

mcg, as a single inhaler) 1 puff twice daily and as needed for asthma management. Asthma exacerbations were managed with oral prednisolone (0.5 mg/kg/day) for seven days.

Sample size: Given the absence of any previous data on combination therapy, we assumed that the combination therapy would decrease the exacerbation rate by an additional ten percent compared to the prednisolone group. In the largest dataset available, the exacerbation rate in ABPA is about 40%.[11] For detecting a 10% decrease in the exacerbation rate (from 40% to 30%), the estimated sample size was 752 subjects (an α error probability of 0.05 and a study power of 80%). For an exploratory study, we took at an effect size of 0.25 (an α error probability of 0.05 and a study power of 90%) with an estimated sample size of 80 participants in each group. After adjusting for a 20% attrition rate, we targeted the randomization of 190 subjects.

Randomization: We randomly assigned study participants in a 1: 1 ratio to receive either prednisolone alone or a combination of prednisolone and itraconazole. The randomization sequence was computer-generated, and we placed the assignments in opaque sealed envelopes. The treating physician at the Chest Clinic assigned the study subject to either of the treatment arms. The study was not blinded.

Statistical analysis: We used the statistical packages SPSS (version 21; IBM Inc., Chicago, IL), StatsDirect (StatsDirect, version 3.3, England, StatsDirect Ltd, 2005. http://www.statsdirect.com), and Medcalc (version 20.0.7, Medcalc software, Ostend, Belgium) to perform the statistical analysis. Data are presented as mean (with standard deviation [SD] or 95% confidence intervals [CI]), median (with interquartile range [IQR]), or numbers with percentage. We compared the categorical and continuous variables using the chi-square test (or Fisher's exact test) and the student's t-test (or Mann-Whitney U test), respectively. We analyzed the time to first exacerbation using the Kaplan-Meier analysis and used the log-rank test to evaluate the difference between the two treatment arms. We performed an exploratory post hoc analysis and report the relative risk of various factors associated with ABPA exacerbation at one and two years of

treatment initiation. Statistical significance was assumed at a p-value of less than 0.05. All p-values are two-sided and are presented without adjustment for multiple testing.

RESULTS

Baseline characteristics: We screened 325 subjects of ABPA between May 2014 and July 2017 (Figure 1). Of these, we randomized 191 to receive either prednisolone alone (n=94) or prednisolone-itraconazole combination (n=97). All the randomized subjects received the intended treatment and completed one year of follow-up; 14 patients were lost to follow-up at 2-years (Figure 1). The mean (standard deviation) age of the study participants was 35.2 (12.4) years, and 56.5% (n=108) were women (Table 1). The study subjects had asthma for a mean (SD) duration of 12.9 (9.5) years before enrollment in the study. The baseline clinical characteristics were similar in both the study groups, except for lower mean body weight in the prednisolone monotherapy than the combination arm (53.1 vs. 57 kg, respectively; p=0.04). We encountered an abnormal chest radiograph or CT chest in 68.6% and 97.4% of the participants, respectively. Bronchiectasis was the most common abnormality on CT (n=180, 94.2%) chest and involved a median (IQR) of 9 (5-12) segments. We observed high-attenuation mucus in 78 (40.8%) of the study subjects. Sputum grew *Aspergillus spp.* in 51 (26.7%) of the study subjects. The imaging abnormalities, immunological parameters, and spirometry findings were similar in the two groups (Table 1). All study subjects received asthma treatment with inhaled corticosteroids and long-acting β2 agonists, while 38% also received montelukast. The dose of inhaled corticosteroids was similar in the two groups (Table 1). The mean (SD) duration of follow-up of the study population was 36.4 (12.8) months; however, we performed all the analyses till two years of follow-up.

Primary outcomes: The proportion of subjects experiencing ABPA exacerbation within 1-year of treatment initiation was 33% and 20.6%, respectively, in the prednisolone monotherapy and prednisolone-itraconazole combination groups (p=0.054). None of the study subjects progressed

to glucocorticoid-dependent ABPA within two years of treatment initiation. Eighty-four subjects experienced ABPA exacerbation at two years of completing initial treatment, and the proportion was not different between the study groups (48.9% vs. 39.2%; p=0.17).

Secondary outcomes: All the study participants in both the study groups satisfied the criteria for a composite response at six weeks of treatment (Table 2). The decline in serum total IgE at six weeks was similar in the control (47.6%) and the intervention arm (45.5%). The mean time to first ABPA exacerbation was 417 days and was not different (p value=0.43, log-rank test) between the study groups (Figure 2). The FEV1 improved by about 300 mL in either group; however, the improvement was not different between the two study groups (Table 2).

Treatment-related AEs: We detected an AE in 78.7% and 73.2% of the subjects in the prednisolone monotherapy and the prednisolone-itraconazole combination groups, respectively (p=0.37). The proportion of subjects experiencing various AEs related to prednisolone was similar in both the study groups (Table 2). Deranged liver function tests were significantly more common in subjects receiving combination therapy (21.6% vs. 6.2%; combination vs. monotherapy). However, none required discontinuation of therapy due to AEs.

Exploratory analysis: We also performed an exploratory post hoc analysis to evaluate the factors associated with ABPA exacerbation at 1-year (Figure 3) and 2-years (Figure S1) after treatment initiation. We found peripheral blood eosinophil count ≥1000 cells/µL, extensive bronchiectasis (≥10 segments), and the absence of HAM to be associated with a lower exacerbation rate at 1-year using the combination therapy. The exacerbation rate at two years (Figure S1) in the combination therapy arm was significantly lower than prednisolone alone in the subgroup of patients with peripheral blood eosinophilia (≥1000 cells/µL) and raised *A.fumigatus*-IgG values (≥100 mgA/L). We discerned no relationship between combination therapy and spirometric (FEV1% predicted), other immunological (serum total IgE, *A.fumigatus*-IgE), microbiological, or imaging findings on exacerbation rate at two years.

DISCUSSION

Although we found no statistical difference in the 1-year exacerbation rate in the prednisolone-itraconazole group versus corticosteroid alone, the trial met our assumption that the combination therapy decreases the exacerbation rate by greater than ten percent as opposed to prednisolone monotherapy. The response rates and the decline in IgE values after 6-weeks were similar in the two groups. While the adverse events were similar in both groups, asymptomatic transaminitis was higher in the itraconazole group. A combination of glucocorticoids and itraconazole is widely believed to be superior to prednisolone or itraconazole monotherapy. The Infectious Disease Society for America (IDSA) guidelines suggest a combination therapy in the treatment of ABPA.[12] Nevertheless, the combination therapy has not been systematically evaluated till recently. One recent study suggested the utility of the combination of itraconazole and prednisone in cystic fibrosis and ABPA; however, the study was not randomized.[13] To our knowledge, the current study is the first RCT on combination therapy in ABPA.

The central tenet of managing ABPA includes glucocorticoids for decreasing pulmonary inflammation and antifungal triazoles for reducing the fungal burden in the airways.[14] The clinical response and IgE decline at six weeks in the current study reflect the profound anti-inflammatory effect of glucocorticoids. We believe that the lower exacerbation rates in the combination group suggest the role of itraconazole in decreasing the fungal burden. The trend in favor of the combination arm could also be explained by the fact that itraconazole is a potent CYP3A4 inhibitor and can increase inhaled budesonide or fluticasone levels.[15, 16] Thus, an imbalance in the arms of CYP3A4 inhibition could contribute to the better efficacy of the combination. The absence of benefit at two years possibly indicates the limited period of action of azole therapy with subsequent recolonization of the airways by *A.fumigatus* in the longer term.

ABPA is a chronic disorder typified by recurrent exacerbations. One of the critical goals of therapy in ABPA is to reduce the risk of exacerbation; hence, we chose this as the primary endpoint.

Only a few randomized trials have evaluated therapies in acute-stage ABPA.[17-19] In the first RCT, a lower dose of glucocorticoid (3-5 month therapy with oral prednisolone starting at 0.5 mg/kg/day) was found to be as effective as a higher dose (8-10 month course with oral prednisolone starting at 0.75 mg/kg/day) in preventing exacerbations after 1-year and 2-years, with lesser side-effects. However, the response rates at six weeks were lower in the low-dose arm (88% vs. 100%).[17] Another RCT found itraconazole (200 mg twice daily for four months) to be associated with a lower response rate (88% vs. 100%) at six weeks compared to oral prednisolone for four months (with an initial dose of 0.5 mg/kg/day). After excluding the early failures, the exacerbations after 1-year and 2-years were similar in the two groups.[19] In the third RCT, voriconazole was found to be as effective as oral prednisolone, with a similar adverse event profile.[18] We chose a slightly higher oral prednisolone dose (than the lower-dose protocol[17]) for the current study based on the experience of the previous RCTs demonstrating a good response at six weeks.[18, 19]

What are the clinical implications of the current study in managing acute-stage ABPA? The results of the current study suggest that patients of treatment-naïve acute-stage ABPA treated with prednisolone-itraconazole combination may have a lower exacerbation frequency at 1-year than prednisolone monotherapy. Further, the combination therapy was beneficial in specific subgroups (patients with peripheral blood eosinophil count ≥1000 cells/µL and those with bronchiectasis involving ≥10 segments on CT), which needs to be explored in future studies. It is possible that due to the small sample size of the current study, we did not achieve a statistically significant benefit with the combination therapy, despite a difference (more than our initial hypothesis) in the exacerbation rates. Also, two previous trials on itraconazole and voriconazole monotherapies found them to be nearly as effective as prednisolone.[18, 19] Based on all these

observations, one approach could be the use of triazole monotherapy as the initial choice and glucocorticoids or the combination of itraconazole-prednisolone reserved for non-responders or in specific subgroups mentioned above. This treatment approach would maximize the efficacy-to-safety ratio. However, a three arm-trial comparing itraconazole, prednisolone, and their combination would resolve the uncertainty on the choice of primary therapy for acute stage ABPA.

Finally, our study has a few limitations. The present research is a single-center study with ABPA patients at the most severe end of the spectrum characterized by extensive bronchiectasis and high-attenuation mucus. The results may be different in less severe cases. We were not able to perform therapeutic drug monitoring for itraconazole. It is known that itraconazole is associated with variable bioavailability.[13] To ensure the best possible gastric absorption, we instructed our patients to take itraconazole with meals or orange juice and avoid antacids and calcium supplements. Finally, the results of our trial may not apply to patients with cystic fibrosis.

In conclusion, we found that the combination of oral prednisolone and itraconazole led to a non-significant reduction in ABPA exacerbations at 1-year than prednisolone monotherapy. Larger studies are required to validate our findings.

Table 1: Baseline characteristics of the study population

	Prednisolone group (n= 94)	Prednisolone-itraconazole group (n= 97)
Demographic variables		
Age, in years	34.1 (12.4)	36.2 (12.4)
Female sex, n (%)	57 (60.6)	51 (52.6)
Height, in cm	161.0 (9.4)	162.4 (9.5)
*Weight, in kg	53.1 (11.4)	57 (13.6)
Duration of asthma, in years	11.8 (9.4)	13.8 (9.6)
Hemoptysis, n (%)	30 (31.9)	32 (33)
Brownish-black mucus plugs, n (%)	16 (17)	18 (18.6)
Spirometry		
FEV1, in liters	1.73 (0.69)	1.78 (0.80)
FVC, in liters	2.55 (0.81)	2.62 (0.87)
FEV1/FVC	66.0 (14.8)	65.0 (12.8)
Severity of obstruction, n (%)		
Normal (FEV1 >80%)	23 (25)	22 (22.7)
Mild obstruction (FEV1 60-80%)	34 (37)	29 (29.9)
Moderate obstruction (FEV1 40-60%)	21 (22.8)	31 (32.0)
Severe obstruction (FEV1 <40%)	14 (15.2)	15 (15.5)
Chest radiograph findings, n (%)		
Any abnormality	61 (64.9)	70 (72.2)
Fleeting opacities	39 (41.5)	47 (48.5)
CT chest findings, n (%)		
Normal HRCT (Serologic ABPA)	2 (2.1)	3 (3.1)
Bronchiectasis	88 (93.6)	92 (94.8)
High-attenuation mucus	39 (41.5)	39 (40.2)
[a]Number of segments involved by bronchiectasis	10 (5.8-13)	8 (5-11)
Immunological findings		
Aspergillus skin test, n/N (%)	83/91 (91.2)	85/95 (89.5)
[b]*A.fumigatus*-specific IgE levels, kUA/L	37.7 (31.8-43.6)	35.1 (30.0-40.2)
[b]*A.fumigatus*-specific IgG levels, mgA/L	95.0 (82.1-107.9)	84.4 (72.2-96.6)
[b]Total IgE levels, IU/mL	10221 (8800-11642)	8950 (7461-10440)
[b]Total eosinophil count, cells/µL	1337 (1064-1610)	1106 (863-1350)
Aspergillus precipitins, n/N (%)	37/89 (41.6)	29/96 (30.2)
Sputum cultures, n (%)		
A.fumigatus	12 (12.8)	8 (8.2)
A.flavus	16 (17)	15 (15.5)
No growth	18 (19.2)	20 (20.6)
No sputum	48 (51.1)	54 (55.7)
Asthma treatment		
Subjects on ICS, n (%)	94 (100)	97 (100)
Dose of ICS (BDPE), µg/day	416 (269)	368 (229)
Subjects on LABA, n (%)	94 (100)	97 (100)
Dose of formoterol, µg/day	13.9 (6.2)	14.5 (6.5)
Subjects on montelukast, n (%)	33 (35.1)	39 (40.2)

All values are presented as mean (standard deviation) unless otherwise stated as n (%), [a]median (1^{st} – 3^{rd} quartile) or [b]mean (95% confidence interval).

ABPA- allergic bronchopulmonary aspergillosis; BDPE- beclomethasone dipropionate equivalent; FEV1- forced expiratory volume in the first second; FVC- forced vital capacity; HRCT- high resolution computed tomography; ICS- inhaled corticosteroids; IU- international units; kUA- kilounits of antibody; LABA- long-acting β2 agonist; LLN- lower limit of normal; mgA - milligrams of antigen-specific antibodies

* p value <0.05

Table 2: Outcomes of the study subjects (n=191) treated with prednisolone or itraconazole and prednisolone

	Prednisolone group (n= 94)	Prednisolone-itraconazole group (n= 97)	Estimate difference (95% CI)	P value
Primary outcomes				
Number of subjects experiencing exacerbation after 1-year	31 (32.9%)	20 (20.6%)	12.3 (-0.2 to 24.5)	0.054
Number of subjects experiencing glucocorticoid-dependent ABPA after 2 years	0	0	-	-
Secondary outcomes				
Response rates after 6-weeks of treatment	94 (100%)	97 (100%)	0 (-0.04 to 0.04)	1.0
Percentage decline in IgE after 6-weeks of treatment	47.6 (43.3-51.9)	45.6 (41.0-50.1)	2.0 (-4.2 to 8.2)	0.47
Mean time to first exacerbation, days	416.2 (371-461)	417.7 (365-470)	-1.5 (-45.3 to 42.3)	0.84
Adverse events				
Any treatment-related adverse event	74 (78.7%)	71 (73.2%)	5.5 (-6.6 to 17.4)	0.37
Cushingoid facies	70 (74.5%)	70 (72.2%)	2.3 (-10.2 to 14.7)	0.19
Weight gain	37 (39.3%)	36 (37.1%)	2.2 (-11.3 to 15.8)	0.86
Deranged liver functions	6 (6.2%)	21 (21.6%)	15.4 (5.5 to 25.1)	0.001
Hypertension	2 (2.1%)	1 (1.0%)	1.1 (-3.7 to 6.5)	1.0
Hyperglycemia	2 (2.1%)	0	2.1 (-2.0 to 7.4)	0.50
Hirsutism	2 (2.1%)	3 (3.1%)	-1.0 (-6.8 to 4.7)	0.68
Emotional lability	1 (1.1%)	1 (1.0%)	0.1 (-4.6 to 4.8)	1.0
Other outcomes				
Spirometry				
Difference in FEV1 after 6 weeks of treatment mL	341 (286-396)	324 (268-380)	17 (-60 to 94)	0.67
Difference in FVC after 6 weeks of treatment mL	361 (305-417)	342 (281-403)	19 (-63 to 101)	0.65
ABPA exacerbations				
1-year	0.58 (0.45-0.72)	0.43 (0.29-0.58)	0.15 (0.01 to 0.29)	0.14
2-years	1.09 (0.92-1.27)	0.96 (0.79-1.12)	0.13 (-0.04 to 0.3)	0.29
Total number of asthma exacerbations after 2-years	0.79 (0.61-0.97)	0.61 (0.44-0.77)	0.18 (-0.06 to 0.42)	0.14

All values are presented as n (%) or mean (95% confidence intervals), unless otherwise stated

CI- confidence intervals; FEV1- forced expiratory volume in the first second; FVC- forced vital capacity

LEGEND TO FIGURES

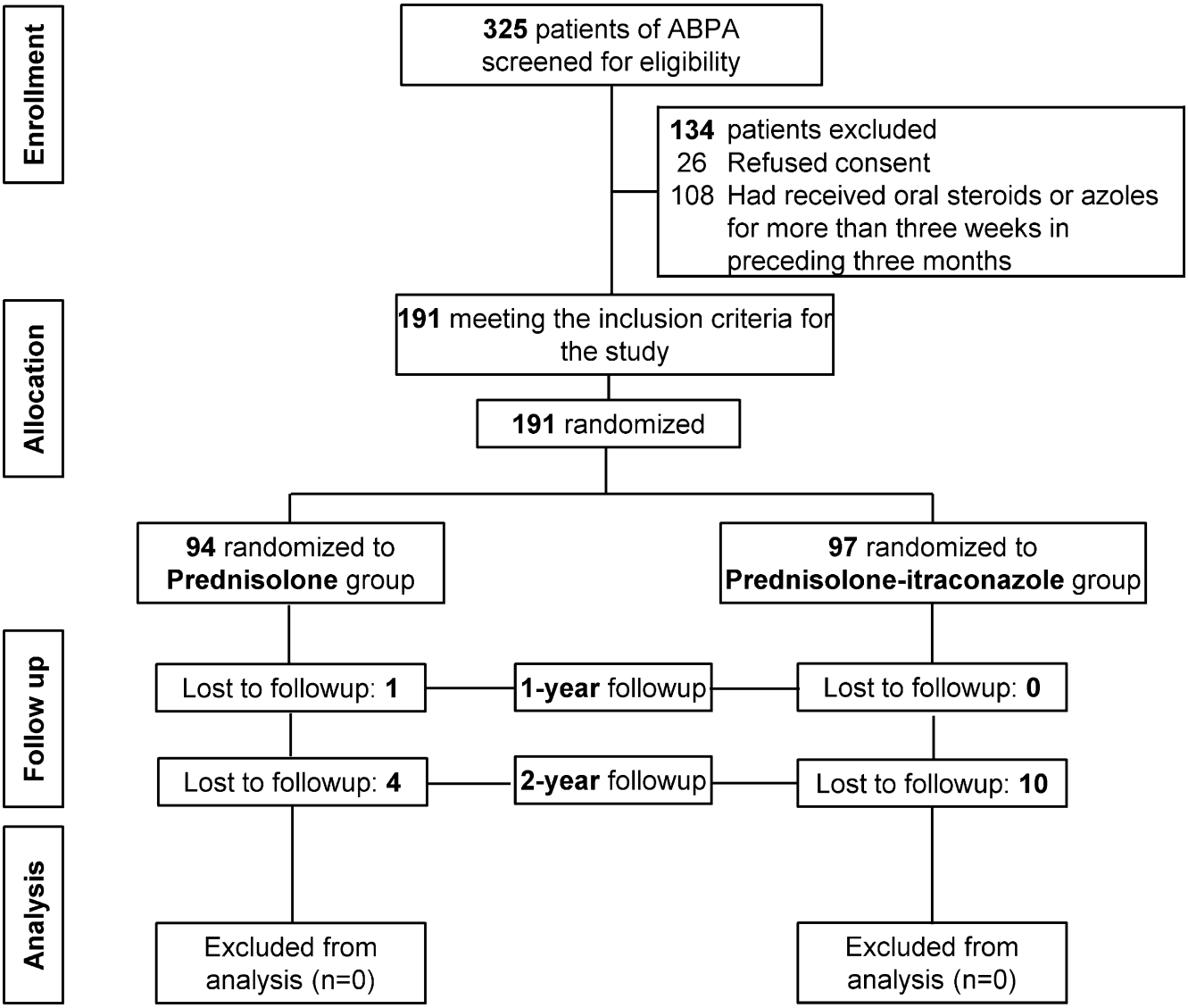

Figure 1: CONSORT diagram depicting the flow of participants in the study (ABPA: allergic bronchopulmonary aspergillosis)

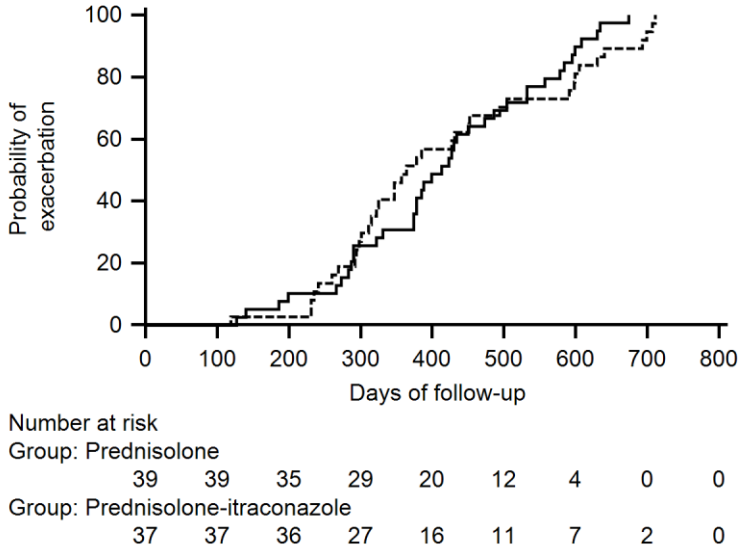

Figure 2: Kaplan-Meier curve demonstrating the probability of exacerbation (vertical axis) against the duration of follow-up in days (horizontal axis). The dotted line represents the prednisolone-itraconazole arm, while the solid line represents the prednisolone monotherapy arm. The mean time to first ABPA exacerbation was 417 days and was not different (p value=0.43, log-rank test) between the study groups

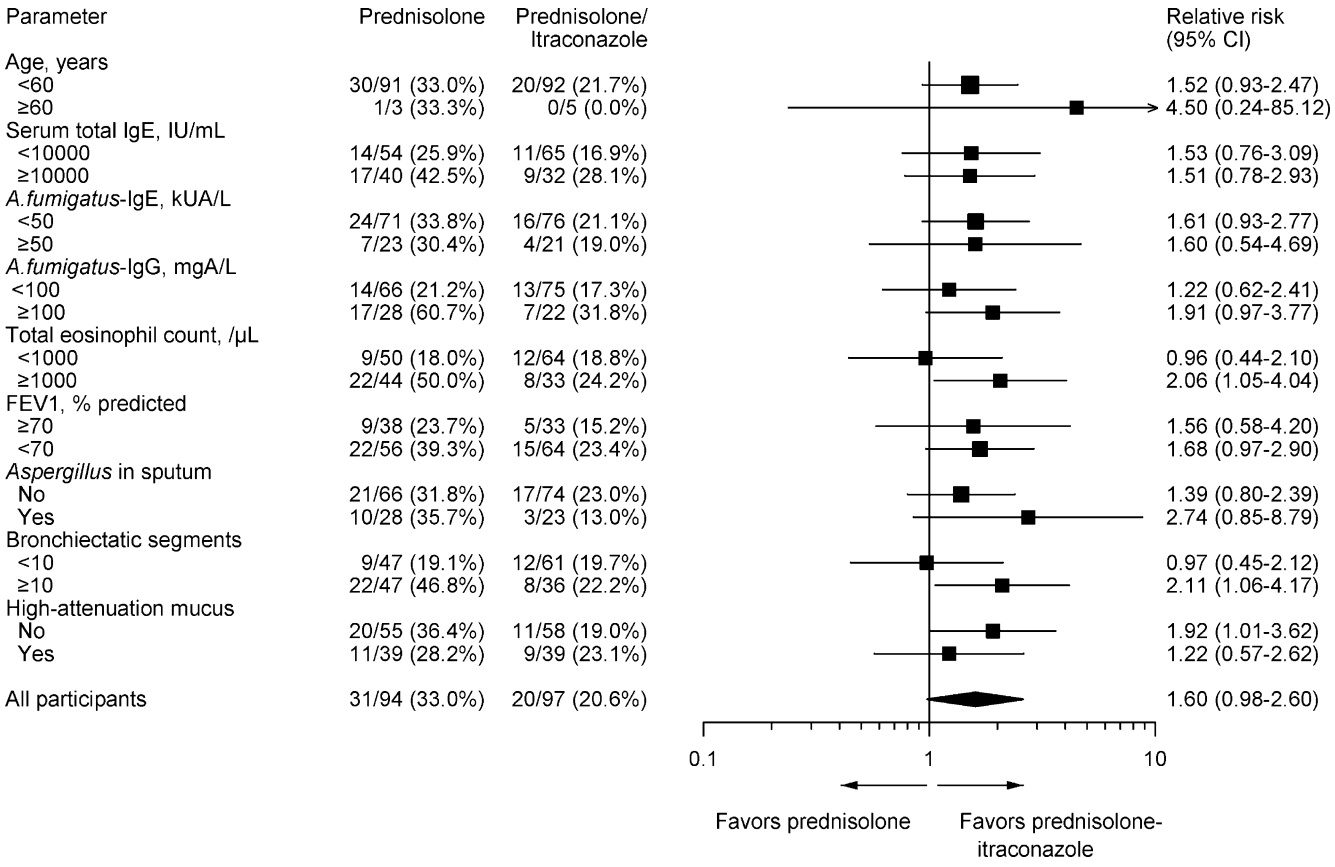

Figure 3: Effect of allocation to prednisolone-itraconazole combination vs. prednisolone alone on 1-year exacerbation rate in a post hoc analysis of various subgroups

Figure S1: Effect of allocation to prednisolone-itraconazole combination vs. prednisolone alone on 2-year exacerbation rate in a post hoc analysis of various subgroups

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Appendix 1

STUDY PROTOCOL

TITLE OF RESEARCH PROJECT

A prospective study on the role of itraconazole in acute stages of allergic bronchopulmonary aspergillosis

INVESTIGATORS

Principal investigator: Dr. Ritesh Agarwal
Additional Professor, Department of Pulmonary Medicine,
Postgraduate Institute of Medical Education and Research,
Chandigarh

Co-investigators: Dr. Ashutosh N Aggarwal
Professor, Department of Pulmonary Medicine,
Postgraduate Institute of Medical Education and Research,
Chandigarh

Dr Sahajal Dhooria
Assistant Professor, Department of Pulmonary Medicine,
Postgraduate Institute of Medical Education and Research,
Chandigarh

Dr. Arunaloke Chakrabarti
Professor, Department of Medical Microbiology,
Postgraduate Institute of Medical Education and Research,
Chandigarh

BACKGROUND

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder caused by a complex hypersensitivity response to antigens released by the fungus *Aspergillus fumigatus*.[1] The clinical entity was first described by Hinson et al in 1952,[2] and the clinical and immunologic significance of *Aspergillus fumigatus* in the sputum were reported by Pepys and coworkers in 1959.[3] The prevalence of ABPA in bronchial asthma is fairly high and a recent meta-analysis suggested the prevalence of ABPA in asthma clinics to be as high as 13 percent.[4] Diagnostic criteria for ABPA have been laid and generally include the following eight major criteria: (a) history of asthma; (b) transient or fixed pulmonary infiltrates; (c) immediate cutaneous hyperreactivity to *A fumigatus* antigen; (d) absolute eosinophil count > 1000/µL; (e) serum precipitins against *A fumigatus*; (f) total IgE levels > 1000 IU/mL; (g) central bronchiectasis on high-resolution computed tomography (HRCT) of the thorax; and, (h) raised *A fumigatus* specific IgE or IgG levels.[5] However, none of these are specific for ABPA.[6-14] Moreover, there is still no consensus on the number of criteria needed for diagnosis, and patients in different stages of ABPA may not fulfill all these criteria.[1,6,15] Recently, we have proposed new criteria for diagnosis and classification of ABPA.[16] Similarly, there is no established definition for remission of ABPA. The most widely followed criteria are clinical and radiological improvement with at least 35 percent decline in total serum IgE levels.[17] However, in a recent study we demonstrated that a 35% decline in serum IgE levels at six weeks is not seen in all patients with ABPA, and the decline is slower in patients with baseline IgE levels <2500 IU/mL.[18] Moreover, the quantum decline in serum IgE levels did not predict clinical outcome.[18] The disorder is highly prevalent in India. We have previously reported our experience with screening stable

outpatients with bronchial asthma and acute severe asthma for ABPA.[18-20] We have also recently reported the prognostic factors associated with clinical outcomes in patients with ABPA.[21,22]

The management of ABPA includes two important aspects – institution of immunosuppressive therapy in the form of glucocorticoids to control the immunologic activity, and close monitoring for detection of relapses. Another possible target is to use antifungal agents to attenuate the fungal burden secondary to the fungal colonization in the airways. Oral corticosteroids are currently the treatment of choice for ABPA associated with bronchial asthma.[1,15,23] They not only suppress the immune hyperfunction but are also anti-inflammatory. However, there is no data to guide the dose and duration of glucocorticoids and different regimens of glucocorticoids have been used in literature.[19,24] Itraconazole, an oral triazole with relatively low toxicity, is active against *Aspergillus* spp. in vitro and in vivo.[25] The activity of itraconazole against *Aspergillus* spp. is more than that of ketoconazole. The administration of itraconazole can eliminate *Aspergillus* in the airways and can theoretically reduce the allergic responses in ABPA.[26-39] We hypothesize that itraconazole when given in the acute stages of ABPA will decrease the chances of relapse and progression to glucocorticoid-dependent ABPA.

OBJECTIVE OF THE STUDY

The aim of this prospective study is to evaluate the efficacy and safety of itraconazole therapy in acute stage of ABPA.

METHODOLOGY

The present study will be a prospective, open-label study, and will include all consecutive patients of ABPA attending the Chest Clinic of this institute. A written consent will be obtained from all patients before randomization and the study will be cleared by the Institute Ethics Committee. Patients, providers, and the investigators who will assess trial outcomes will not be blinded to treatment assignment.

Patients: We prospectively screen all consecutive patients with asthma presenting to the Chest clinic with an aspergillus skin test. Patients will be eligible for inclusion in the study if they meet the criteria for ABPA defined by the presence of all the following: (a) asthma; (b) immediate cutaneous hyperreactivity on *Aspergillus* skin test or *A.fumigatus* specific IgE levels >0.35 kUA/L; (c) elevated total IgE levels >1000 IU/mL; and, two of the following features: (a) presence of precipitating antibodies against *A.fumigatus* in serum; (b) fixed or transient radiographic pulmonary opacities; (c) total eosinophil count >1000/µL; and, (d) bronchiectasis on HRCT chest. Patients with any of the following will be excluded: (a) intake of systemic glucocorticoids for more than three weeks in the preceding six months; (b) exposure to azoles in the last six months; (c) immunosuppressive states such as uncontrolled diabetes mellitus, chronic renal failure, chronic liver failure and others; (d) patient on immunosuppressive drugs; (e) pregnancy; (f) enrollment in another trial of ABPA; and, (g) failure to provide informed consent.

Patients will be further classified on the basis of HRCT into serologic ABPA (ABPA with normal HRCT of the chest), ABPA with bronchiectasis (ABPA-B), ABPA with high-attenuation mucus (ABPA-HAM).[16,22]

Randomization: The patients will be randomly assigned to treatment with glucocorticoid (group I) or glucocorticoid plus itraconazole (group II). The randomization sequence will be computer generated, and the assignments will be placed in sealed opaque envelopes and each patient's assignment will be made by the treating physician in the Chest Clinic. The study will not be blinded. Data will be collected in clinical record forms, entered into a computerized database, and will be validated against the record books before analysis. The hospital data safety and monitoring board will be apprised about the serious adverse events on a continuous basis.

Study procedure: All patients fulfilling the criteria for ABPA will be randomized into the following two groups:

Group I (steroid arm) – oral prednisolone 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks and discontinue by the end of 4 months**.** Patients will also receive inhaled formoterol/fluticasone (6/125 mcg) 1 puff BD and as needed as per the SMART approach[40] for control of asthma.

Group II (itraconazole arm) – oral itraconazole 200 mg BD for 6 months**.** Oral prednisolone 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks and discontinue by the end of 4 months. Patients will also receive inhaled formoterol/fluticasone (6/125 mcg) 1 puff BD and as needed as per the SMART approach[40] for control of asthma.

Endpoints: We will collect the following data: 1. detailed clinical history (especially age, gender, duration of asthma, history of hemoptysis, expectoration of brownish-black mucus plugs and history of anti-tuberculous therapy) and physical examination; 2. immunological test results (serum total IgE, *A.fumigatus*-specific IgE and IgG, *A.fumigatus* precipitins, and peripheral blood

eosinophil count); (3) spirometry (forced expiratory volume in the first second [FEV1] and forced vital capacity [FVC]); and (4) chest radiograph and CT chest findings.. Patients will be followed up with history and physical examination, chest radiograph and serum IgE levels (total) at each visit every six weeks.

Clinical improvement in cough and dyspnea will be documented subjectively on a four-point scale as 1: no improvement or worsening; 2: mild improvement (up to 25% of baseline); 3: moderate improvement (25%-75% of baseline); 4: significant improvement (>75% of baseline).

The treatment effects will be classified as:

(a) **response**: defined on the basis of a composite clinical, radiological and immunological criteria when there was improvement in cough and dyspnea (>75% of baseline) **and** the IgE levels declined by more than 25% accompanied by partial/total clearance of chest radiographic lesions (if present prior to treatment initiation) after six weeks of glucocorticoids.

(b) **relapse**: doubling of the baseline IgE levels irrespective of the patient's symptoms or appearance of radiologic infiltrates; or clinical and/or radiological worsening with 50% increase in IgE over the previous baseline value.

(c) **glucocorticoid-dependent ABPA**: if the patient has relapse on two or more consecutive occasions within 6 months of stopping treatment or requires oral steroids for control of asthma.

(d) **asthma exacerbation**: defined as worsening of cough or dyspnea in the absence of immunological or radiological worsening of ABPA.

The ***primary outcomes*** will be: (b) relapse rates within 12 months of initiating glucocorticoid therapy; and, (b) progression to glucocorticoid-dependent ABPA after 24 months of treatment.

The ***secondary outcomes*** were: (a) proportion of patients with a response rates (as defined above) at six weeks of treatment; (b) percentage decline in IgE (baseline IgE minus IgE after six weeks/baseline IgE) after six weeks of treatment (c) time to first relapse; and, (d) treatment-related adverse effects.

Treatment of ABPA relapses (exacerbations): We will treat the first exacerbation with prednisolone, while the subsequent exacerbations will be managed with a combination of prednisolone and itraconazole, at doses in groups 1 and 2. We will use voriconazole in subjects' intolerant to itraconazole.

Treatment of asthma and asthma exacerbations: For the management of asthma, we will use inhaled formoterol/fluticasone (6/125 mcg, as a single inhaler) 1 puff twice daily and as needed. Leukotriene receptor antagonist (montelukast), in both the groups, at discretion of the treating physician. Asthma exacerbations will be managed with oral prednisolone (0.5 mg/kg/day) for seven days.

The concomitant use of medications for treatment of ABPA such as itraconazole, voriconazole, inhaled amphotericin B, or omalizumab will not be permitted. Use of inhaled corticosteroids for control of asthma will be allowed.

Statistical analysis: Statistical analysis will be performed using the statistical package SPSS for MS Windows (version 10; SPSS Inc.; Chicago, IL) and StatsDirect (StatsDirect, version 2.7.2 for MS-Windows, England, StatsDirect Ltd, 2005. http://www.statsdirect.com). Data will be presented in a descriptive fashion as mean (95% confidence intervals [CI]) or percentage (95% CI). Categorical variables will be compared using the chi-square test while Mann-Whitney U test will be used as applicable in case of continuous variables. Statistical significance will be assumed at a p-value of less than 0.05.

ETHICAL CONSIDERATIONS

All the patients attending Chest Clinic will receive treatment protocols that have been evaluated for their safety. A written and informed consent will be taken from the patients before randomization into the study. The information collected will not be of any personal nature, and patient confidentiality will not be breached in any fashion. No investigator has any financial or other conflicts of interests to declare. The patient is also free to opt out of the study at any time without having to give any reason and this will not affect his future treatment in the hospital.

REVIEW OF LITERATURE

Aspergillus is a ubiquitous mold representing between 0.1 and 22 percent of the total air spores sampled.[41] There are approximately 250 species of *Aspergillus* but only a few are human pathogens.[42,43] Depending on the host immunity and the organism virulence, the respiratory diseases caused by *Aspergillus* are classified as saprophytic (aspergilloma), allergic (allergic aspergillus sinusitis, allergic bronchopulmonary aspergillosis (ABPA) and hypersensitivity pneumonias) and invasive (airway invasive aspergillosis, chronic necrotizing pulmonary aspergillosis and invasive aspergillosis).[44] ABPA is an allergic pulmonary disorder caused by hypersensitivity to *Aspergillus fumigatus* (*Af*) clinically manifesting as chronic asthma, recurrent pulmonary infiltrates, and bronchiectasis.[23,24,45-51] The condition has immunologic features of immediate hypersensitivity (type I), antigen-antibody complexes (type III), and eosinophil-rich inflammatory cell responses (type IVb), based on the revised Gell and Coombs classification of immunologic hypersensitivity.[52,53] The disorder was first described by Hinson in 1952 in the United Kingdom.[2] Occasionally, patients can develop a syndrome similar to ABPA but is caused by fungi other than *Af* and is termed as allergic bronchopulmonary mycosis.[54] The condition remains underdiagnosed in many countries with reports of mean diagnostic latency of ten years between the occurrence of symptoms and the diagnosis.[55] In the past two decades, there has been an increase in the number of cases of ABPA due to the heightened physician awareness and the widespread availability of serologic assays.[19,21,56-58]

Glucocorticoids are the drug treatment of choice for ABPA. They not only suppress the immune hyperfunction but are also anti-inflammatory. Although small case studies suggest some benefit of inhaled corticosteroids (ICS) in management of ABPA,[59-62] a double blind

multicenter placebo controlled trial in 32 patients suggested no superiority over placebo.[63] However, this study used low doses of ICS (400 mcg beclomethasone per day) and spacers were not used. We have also found no benefit with the use of ICS.[64] Currently there is no role of low dose ICS in the management of ABPA, and further investigations are required to ascertain the potential benefits of high doses of ICS. The clinical effectiveness of any therapy in ABPA is reflected by marked decreases in the patient's total serum IgE levels (there seems to be no correlation between serum levels of *A fumigatus* specific IgE levels and disease activity[27]) along with symptom and radiographic improvements. The goal of therapy is not to attempt normalization of IgE levels but to decrease the IgE levels by 25 to 30 percent which in most cases leads to clinical and radiographic improvement.[18] One should also aim to establish a stable baseline serum level of total IgE which serves as a guide to future detection of relapse and helps in follow-up of the patient.

The use of specific antifungal agents in ABPA has the advantage of modifying the immune response by removing/reducing the antigenic stimulus consequent to a decreased fungal burden. Ketoconazole has been tried in the past[65] and has been replaced by the less toxic agent, itraconazole.[26-29,31-38,66-68] Oral itraconazole has been shown to benefit patients with ABPA, in part by reducing the need for systemic steroids.[26-29,31,34] Two randomized controlled studies (84 patients) have evaluated the role of itraconazole in ABPA.[35,38] In one study, 55 patients with 'glucocorticoid-dependent' ABPA were randomized to receive either itraconazole 200 milligrams twice a day versus placebo. The difference between the two groups was significant in terms of overall response (reduction in the dose of corticosteroid by 50 percent or more; and, decrease in the total IgE concentration by 25 percent or more; and, at least one of

the following [increase in exercise tolerance by at least 25 percent, improvement by 25 percent in results of the pulmonary function tests, resolution of pulmonary infiltrates]) but failed to reach statistical significance when each of the outcomes were examined separately.[35] The other study included 29 'clinically stable' ABPA patients randomized to receive itraconazole or placebo. Interestingly, majority of the patients did not receive glucocorticoids. There were significant decline in sputum inflammatory markers and serum IgE levels. The study also demonstrated a decrease in the number of exacerbations warranting glucocorticoid usage.[38] Pooled analysis showed that itraconazole could significantly decrease the IgE levels by 25 percent or more when compared to placebo but did not cause significant improvement in lung function.[69]

Based on the results of these two RCTs, itraconazole is approved for use in ABPA. However, both the studies were conducted either in glucocorticoid-dependent ABPA or patients who had already been treated for ABPA with steroids. Thus no study has systematically evaluated the role of itraconazole in acute stages of ABPA, especially its long-term benefits. This project attempts to study the role of itraconazole in acute stages of ABPA.

Evaluations at study visits

	Visit 1	Visit 2 (0 wk)	Visit 3 (6 wk)	Visit 4 (12 wk)	Visit 5 (18 wk)	Visit 6 (24 wk)	Visit 7 (12 mo)	Visit 8 (18 mo)	Visit 9 (20 mo)
Screening	**x**								
Randomization		**x**							
Clinical symptoms	**x**			**x**	**x**	**x**	**x**	**x**	**x**
Physical examination	**x**			**x**	**x**	**x**	**x**	**x**	**x**
Serum total IgE	**x**			**x**	**x**	**x**	**x**	**x**	**x**
A.fumigatus IgE	**x**								
A.fumigatus IgG or A.fumigatus precipitins	**x**								
Eosinophil count	**x**								
Spirometry	**x**		**x**						
Chest X-ray	**x**		**x**	**x**	**x**	**x**			
CT chest	**x**								

Adverse effects of treatment (at all visits)

	Visit 3	Visit 4	Visit 5	Visit 6
Abdominal				
Abdominal pain				
Dyspepsia				
Others				
Appearance and skin				
Cushingoid facies				
Acne				
Skin thinnning				
Easy bruising/purpura				
Alopecia				
Hypertrichosis				
Visual disturbances* (Describe)				
Mental				
Cognitive impairment				
Mood changes (describe)				
Insomnia				
Hormonal				
Amenorrhoea				

Other AEs				
Avascular necrosis				
Myopathy				
Infection				
Others				
LFT abnormalities				

***If present, evaluate for central serous retinopathy, cataract, and glaucoma and describe.**

CONSENT PROFORMA

TITLE: A prospective study on the role of itraconazole in acute stages of allergic bronchopulmonary aspergillosis

AIMS: This is a research project to evaluate the efficacy and safety of two different treatment protocols in Allergic Bronchopulmonary Aspergillosis

INVESTIGATORS: The study will be conducted by Dr Ritesh Agarwal, Additional Professor, Department of Pulmonary Medicine, PGIMER, Chandigarh along with Dr. Ashutosh N Aggarwal, Professor, Department of Pulmonary Medicine, PGIMER, Chandigarh, Dr. Sahajal Dhooria, Assistant Professor, Department of Pulmonary Medicine, PGIMER, Chandigarh, and Dr. Arunaloke Chakrabarti, Professor, Department of Medical Microbiology, PGIMER, Chandigarh.

FUNDING: The study is investigator-initiated and is not funded by any funding agency.

STUDY PROPOSED: 190 patients (95 each in two arms) of ABPA will be randomized to receive either itraconazole plus glucocorticoids or glucocorticoids alone. **The consent to participate in this research is voluntary and the patient maintains the right to withdraw from the study**. The records will be maintained confidentially.

BENEFITS FROM THIS STUDY: This study aims to understand the efficacy and safety of two different treatment protocols in allergic bronchopulmonary aspergillosis.

POSSIBLE RISKS: All the patients attending Chest Clinic will receive the standard of care treatment. Further both the treatment protocols have been evaluated for their safety and **no added risk** will be incurred by the patient.

I _____ hereby state that I have been explained the need, benefits, methodology and potential risks of this study, in a language understood by me. I give full consent for the same.

Date Signature

PATIENT INFORMATION SHEET

INVESTIGATOR (Principal and at least one Co-Investigator): Dr Ritesh Agarwal, Dr Ashutosh N Aggarwal

Name of Participant:

Title: A prospective study on the role of itraconazole in acute stages of allergic bronchopulmonary aspergillosis

You are invited to take part in this research study. The information in this document is meant to help you decide whether or not to take part. Please feel free to ask if you have any queries or concerns.

You are being asked to participate in this study being conducted in Postgraduate Institute of Medical Education and Research, Chandigarh because you satisfy our eligibility criteria which are:

(1) Diagnosis of allergic bronchopulmonary aspergillosis

(2) Age between 12 to 65 years

(3) No contraindication to the use of the agents to be used in the study, which means absence of any disease or condition likely to get worsened by the drugs under study, which are chronic liver disease, acute and chronic active hepatitis. Other contraindications are failure to give informed consent, intake of glucocorticoids for more than three weeks in the preceding six months, enrollment in another trial of ABPA and any exposure to azoles in the last six months.

(4) Neither pregnant nor breast-feeding in case of female patients

You will be one of the 190 patients we plan to recruit in this study. You will be assigned to either of the two study groups. One group of patients will receive control medication(s), which

are oral glucocorticoids while other group of patients will receive oral itraconazole and glucocorticoids. The drug itraconazole is being used so that we can compare its effect in maintaining remission compared to steroids.

What is the purpose of research?

Allergic bronchopulmonary aspergillosis is a disorder characterized by uncontrolled asthma and progression to end-stage lung disease. It usually presents with cough, dyspnea, fever, anorexia, weight loss and wheezing. These symptoms may last for months to years. The disease is caused by allergy to a fungal agent called Aspergillus fumigatus. If untreated the disease progresses to end-stage lung disease characterized by bronchiectasis and respiratory failure. The present treatment for this disease is glucocorticoids.

We want to test the efficacy and safety of itraconazole in maintenance of remission in this disease. This drug has been found to possess good activity in earlier human studies. The proposed benefit(s) of new drug over the existing treatment include(s) lesser side-effects with equal or even better efficacy. This drug has been shown to be well tolerated as shown in results obtained from earlier studies done in humans.

In the present study, we plan to see the effect of itraconazole in patients with allergic bronchopulmonary aspergillosis.

Information obtained from this study would be beneficial to other patients with the same disease.

We have obtained permission from the Institutional Ethics Committee for conducting this study.

The study design

All patients in the study will be divided into two groups. You will be assigned to either of the two groups. One group will receive oral itraconazole plus glucocorticoids (study drug) and the other group will receive glucocorticoids for a period of 120 days. Which treatment group you will be assigned to will be determined purely by chance, which, in scientific language, is called 'randomization'. Randomization improves the scientific quality of research. This study will be open-label. This means that the investigator (or you) will be aware of whether you are receiving itraconazole or glucocorticoids.

Study Procedures

The study involves evaluation of investigational drug for which we will be monitoring your symptoms/ IgE levels/CXR every two months for one year.

Once you are enrolled in the study, you will be required to follow the instructions [take the drugs as instructed and detailed on the envelope / avoid alcohol / smoking]. You will be given inhaled medications, which you will need to take two times a day, thrice a week for four months. You will be told about your visit schedules and you will have to report to the hospital (study site). The planned scheduled visits involve visits every eight weeks after your initial visit. You will be required to visit the hospital many number of times during the study. You are not allowed to take any medications other than the ones prescribed by your investigator. If you need to take some treatment, you must consult your investigator before taking that treatment. At each visit, the study physician will examine you. Some blood tests will be carried out at each visit. 5 ml of blood will be collected at each visit. Blood collection involves prick with a needle and syringe.

These tests are essential to monitor your condition, and to assess the safety and efficacy of the treatment given to you. In addition, if you notice any physical or mental change(s), you must contact the persons listed at the end of the document. [You will be required to return unused study medicines when you report for your scheduled visits. This will enable correct assessment of the study results.] You may have to come to the hospital (study site) for examination and investigations apart from your scheduled visits, if required.

Women of childbearing potential

You must not participate if you are pregnant, breastfeeding a child, or if you are of childbearing potential and not practicing two forms of effective methods of contraception. These forms could be an oral contraceptive pill plus a condom or diaphragm; or two barrier methods (e.g. a condom and diaphragm).You may also consider participating, if you are surgically sterile or postmenopausal. If you become pregnant during the study, you or your unborn child may be exposed to risks, which are currently unknown. Your urine will be tested for pregnancy at screening and at each visit for 16 weeks. If the test is positive at any time, you will be withdrawn from the study.

Possible risks to you

Both the drugs have no major side effects. You may have a feeling of nausea while the drug is being administered. The first dose may cause cough and hence the first dose will be administered under supervision. The study drug in earlier studies, has not demonstrated side effects other than nausea, vomiting and first dose bronchospasm. These are temporary, minor and self-limiting and are reversible on discontinuation of medicine. However, it is possible that other rare side effects could occur which are not described here.

Possible benefits to you

You are not expected to get any benefit from being on this research study, other than the treatment benefit.

Compensation: You will not receive any compensation for the inconvenience and travel. You will also not be given any free treatment.

Possible benefits to other people

The results of the research may provide benefits to the society in terms of advancement of medical knowledge and/or therapeutic benefit to future patients.

The alternatives you have

If you do not wish to participate, you have the alternative of getting the standard treatment for your condition. At present, to the best of our knowledge, no other new agent is being tried out for research in humans.

Cost to the participant

You will be required to pay for the medications. In case of any adverse event occurring due to the study medications, you will be provided treatment at our Institute and proper referral if necessary.

Who is paying for this research?

There is no funding involved in this research.

What should you do in case of injury or a medical problem during this research study?

Your safety is the prime concern of the research. If you are injured or have a medical problem as a result of being in this study, you should contact one of the people listed at the end of the

consent form. You will be provided the required care/treatment. You will be entitled to your legal rights besides this.

Confidentiality of the information obtained from you

You have the right to confidentiality regarding the privacy of your medical information (personal details, results of physical examinations, investigations, and your medical history). By signing this document, you will be allowing the research team investigators, other study personnel, sponsors, institutional ethics committee and any person or agency required by law like the Drug Controller General of India to view your data, if required. The results of clinical tests and therapy performed as part of this research may be included in your medical record. The information from this study, if published in scientific journals or presented at scientific meetings, will not reveal your identity.

How will your decision to not participate in the study affect you?

Your decision not to participate in this research study will not affect your medical care or your relationship with the investigator or the institution. Your doctor will still take care of you and you will not lose any benefits to which you are entitled.

Can you decide to stop participating in the study once you start?

The participation in this research is purely voluntary and you have the right to withdraw from this study at any time during the course of the study without giving any reasons. However, it is advisable that you talk to the research team prior to stopping the treatment. You may be advised about how best to stop the treatment safely. If you withdraw, you may be asked to undergo some additional tests to which you may or may not agree. Though advisable that you give the investigators the reason for withdrawing, it is not mandatory.

Can the investigator take you off the study?

You may be taken off the study without your consent if you do not follow instructions of the investigators or the research team or if the investigator thinks that further participation may cause you harm.

Right to new information: If the research team gets any new information during this research study that may affect your decision to continue participating in the study, or may raise some doubts, you will be told about that information.

Contact persons

For further information / questions, you can contact us at the following address:

Principal Investigator Dr. Ritesh Agarwal

Dept. of Pulmonary Medicine

[PGIMER, Sector-12, Chandigarh-160012]

Ph: 7087009825

Contact person(s): Dr. Ritesh Agarwal

Dept. of Pulmonary Medicine

[PGIMER, Sector-12, Chandigarh-160012]

Ph: 7087009825

CASE RECORD FORM

Name	Age
Sex Male Female	Height (cm) Weight (kg)
History of asthma	Yes No
Duration of asthma (years)	
Hemoptysis	Yes No
Brownish-black mucus plugs	Yes No
History of ATT intake If yes- No. of courses:	Yes No
Chest x-ray	Abnormal Normal
Parallel opacities (Y/N) Ring opacities (Y/N) Finger-in-glove (Y/N)	Tram-line opacities (Y/N) Fleeting opacities (Y/N)
Aspergillus skin test T1 T3 T4	 Positive Negative Positive Negative Positive Negative
IgE levels (IU/mL)	
IgE levels (*Af*) (kUA/L)	
Absolute eosinophil count (per µL)	
Aspergillus precipitins	Positive Negative

HRCT chest	Abnormal Normal
Bronchiectasis	
Lobes	RUL RLL RML LUL LLL Total
Segments	RUL- apical anterior posterior RML- medial lateral RLL- apical medial anterior lateral posterior LUL- apicoposterior anterior Lingula- superior inferior LLL- apical anteromedial lateral posterior Total
Presence of high-attenuation mucus	Yes No
Density of mucus (in HU)	HU
Mucus plugging without HAM	Yes No
Centrilobular nodules	Yes No
Tree-in-bud	Yes No
Mosaic attenuation	Yes No
Other findings	

Spirometry

Spirometry	At diagnosis	After remission
Date and number		
FEV1		

FVC		
FEV1/FVC		

Treatment protocol

New cases	
Group 1	**Group 2**
Prednisolone 0.5 mg/kg/day for 4 weeks; then 0.25 mg/kg/day for 4 weeks; then 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks **and discontinue by 4 months** **Total steroid dose received-**	Itraconazole 200 mg BD for 6 mos. Prednisolone 0.5 mg/kg/day for 4 weeks; then 0.25 mg/kg/day for 4 weeks; then 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks **and discontinue by 4 months** **Total steroid dose received-**

Follow-up

Date														
IgE (IU/mL)														
CXR														
Clinical status														

Others														

1: no improvement or worsening; 2: mild improvement (up to 25% of baseline); 3: moderate improvement (25%-75% of baseline); 4: significant improvement (>75% of baseline).

Side-effects

Cushingoid facies	Hypertension	Striae
Hyperglycemia	Hirsutism	Emotional instability
Depression	Weight gain (> 10%)	LFT abnormalities
Others -		

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Appendix 2

Clinical trial registration

ClinicalTrials.gov Protocol Registration and Results System (PRS) Receipt
Release Date: April 25, 2017

ClinicalTrials.gov ID: NCT02440009

Study Identification

Unique Protocol ID:	Histo-15-IMEC-313
Brief Title:	A Randomized Trial of Itraconazole in Acute Stages of Allergic Bronchopulmonary Aspergillosis (RIA)
Official Title:	A Randomized Trial of Itraconazole in Acute Stages of Allergic Bronchopulmonary Aspergillosis
Secondary IDs:	

Study Status

Record Verification:	April 2017
Overall Status:	Recruiting
Study Start:	May 2015 []
Primary Completion:	June 2017 [Anticipated]
Study Completion:	June 2017 [Anticipated]

Sponsor/Collaborators

Sponsor:	Postgraduate Institute of Medical Education and Research
Responsible Party:	Principal Investigator Investigator: Ritesh Agarwal [ragarwal] Official Title: Professor, Department of Pulmonary Medicine, Principal Investigator Affiliation: Postgraduate Institute of Medical Education and Research
Collaborators:	

Oversight

U.S. FDA-regulated Drug:	
U.S. FDA-regulated Device:	
U.S. FDA IND/IDE:	No
Human Subjects Review:	Board Status: Approved Approval Number: 01/04/2015 Board Name: IEC, PGI (Intramural) Board Affiliation: Postgraduate Institute of Medical Education and Research, Chandigarh Phone: 2755141 Email: kakkar.nandita@pgimer.edu.in

Address:	
Data Monitoring:	Yes
FDA Regulated Intervention:	No

Study Description

Brief Summary:	The study evaluates the addition of itraconazole to glucocorticoids in management of acute stages of allergic bronchopulmonary aspergillosis (ABPA). Half of the participants will receive glucocorticoids while the other half will receive itraconazole and glucocorticoids
Detailed Description:	The management of allergic bronchopulmonary aspergillosis (ABPA) includes two important aspects namely institution of immunosuppressive therapy in the form of glucocorticoids to control the immunologic activity, and close monitoring for detection of relapses. Another possible target is to use antifungal agents to attenuate the fungal burden secondary to the fungal colonization in the airways. Oral corticosteroids are currently the treatment of choice for ABPA associated with bronchial asthma. They not only suppress the immune hyperfunction but are also anti-inflammatory. Itraconazole, an oral triazole with relatively low toxicity, is active against Aspergillus spp. in vitro and in vivo. The activity of itraconazole against Aspergillus spp. is more than that of ketoconazole. The administration of itraconazole can eliminate Aspergillus in the airways and can theoretically reduce the allergic responses in ABPA. We hypothesize that itraconazole when given in the acute stages of ABPA will decrease the chances of relapse and progression to glucocorticoid-dependent ABPA.

Conditions

Conditions:	Allergic Bronchopulmonary Aspergillosis
Keywords:	

Study Design

Study Type:	Interventional
Primary Purpose:	Treatment
Study Phase:	Phase 2/Phase 3
Interventional Study Model:	Single Group Assignment
Number of Arms:	2
Masking:	None (Open Label)
Allocation:	Randomized
Enrollment:	150 [Anticipated]

Arms and Interventions

Arms	Assigned Interventions
Active Comparator: Glucocorticoid group	Drug: Glucocorticoids

Arms	Assigned Interventions
Oral prednisolone 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks and discontinue by the end of 4 months. Patients will also receive inhaled formoterol/fluticasone (6/125 mcg) 1 puff BD and as needed as per the SMART approach for control of asthma	Oral prednisolone 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks and discontinue by the end of 4 months. Other Names: • Steroid
Experimental: Itraconazole plus glucocorticoid group Oral itraconazole 200 mg BD for 6 months AND oral prednisolone 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks and discontinue by the end of 4 months. Patients will also receive inhaled formoterol/fluticasone (6/125 mcg) 1 puff BD and as needed as per the SMART approach for control of asthma.	Drug: Itraconazole Oral itraconazole 200 mg BD for 6 months Other Names: • Azole Drug: Glucocorticoids Oral prednisolone 0.5 mg/kg/day for 4 weeks; 0.25 mg/kg/day for 4 weeks; 0.125 mg/kg/day for 4 weeks. Then taper by 5 mg every 4 weeks and discontinue by the end of 4 months. Other Names: • Steroid

Outcome Measures

Primary Outcome Measure:

1. Relapse rates
   Doubling of the baseline IgE levels irrespective of the patient's symptoms or appearance of radiologic infiltrates; or clinical and/or radiological worsening with 50% increase in IgE over the previous baseline value

   [Time Frame: 12 months]
2. Glucocorticoid-dependent ABPA
   If the patient has relapse on two or more consecutive occasions within 6 months of stopping treatment or requires oral steroids for control of asthma

   [Time Frame: 24 months]

Secondary Outcome Measure:

3. Proportion of patients with a response rates
   [Time Frame: Six weeks]
4. Percentage decline in IgE
   [Time Frame: Six weeks]
5. Time to first relapse
   [Time Frame: Two years]
6. Treatment-related adverse effects
   [Time Frame: Six months]

Eligibility

Minimum Age:	18 Years
Maximum Age:	75 Years
Sex:	All
Gender Based:	
Accepts Healthy Volunteers:	No

Criteria: Inclusion Criteria:

Treatment naive patients of allergic bronchopulmonary aspergillosis (ABPA) defined by the presence of all the following:

- asthma
- immediate cutaneous hyperreactivity on Aspergillus skin test or A.fumigatus specific IgE levels >0.35 kUA/L
- elevated total IgE levels >1000 IU/mL and, two of the following features:
- presence of precipitating antibodies against A.fumigatus in serum
- fixed or transient radiographic pulmonary opacities
- total eosinophil count >1000/µL
- bronchiectasis on HRCT chest

Exclusion Criteria:

- Intake of systemic glucocorticoids for more than three weeks in the preceding six months
- Exposure to azoles in the last six months
- Immunosuppressive states such as uncontrolled diabetes mellitus, chronic renal failure, chronic liver failure and others
- Patient on immunosuppressive drugs
- Pregnancy
- Enrollment in another trial of ABPA
- Failure to provide informed consent

Contacts/Locations

Central Contact Person: Ritesh Agarwal, MD, DM
Telephone: 2756825
Email: riteshpgi@gmail.com

Central Contact Backup: Ashutosh N Aggarwal, MD, DM
Telephone: 2756824
Email: aggarwal.ashutosh@outlook.com

Study Officials:

Locations: India
Chest Clinic, PGIMER
[Recruiting]
Chandigarh, India, 160012
Contact: Ritesh Agarwal, MD, DM 0172-2756825 riteshpgi@gmail.com
Contact: Ashutosh Aggarwal, MD, DM 0172-2756824
dr.anaggarwal@gmail.com

IPDSharing

Plan to Share IPD:

References

Citations:

Links:

Available IPD/Information:

Parameter	Prednisolone	Prednisolone/ Itraconazole	Relative risk (95% CI)
Age, years			
<60	45/91 (49.5%)	36/92 (39.1%)	1.26 (0.91-1.76)
≥60	1/3 (33.3%)	2/5 (40.0%)	0.83 (0.12-5.72)
Serum total IgE, IU/mL			
<10000	23/54 (42.6%)	19/65 (29.2%)	1.46 (0.89-2.38)
≥10000	23/40 (57.5%)	19/32 (59.4%)	0.97 (0.65-1.43)
A.fumigatus-IgE, kUA/L			
<50	33/71 (46.5%)	30/76 (39.5%)	1.18 (0.81-1.71)
≥50	13/23 (56.5%)	8/21 (38.1%)	1.48 (0.77-2.85)
A.fumigatus-IgG, mgA/L			
<100	26/66 (39.4%)	30/75 (40.0%)	0.98 (0.65-1.48)
≥100	20/28 (71.4%)	8/22 (36.4%)	1.96 (1.08-3.58)
Total eosinophil count, /μL			
<1000	19/50 (38.0%)	26/64 (40.6%)	0.94 (0.59-1.48)
≥1000	27/44 (61.4%)	12/33 (36.4%)	1.69 (1.01-2.81)
FEV1, % predicted			
≥70	16/38 (42.1%)	10/33 (30.3%)	1.39 (0.73-2.63)
<70	30/56 (53.6%)	28/64 (43.8%)	1.22 (0.85-1.77)
Aspergillus in sputum			
No	31/66 (47.0%)	30/74 (40.5%)	1.16 (0.79-1.69)
Yes	15/28 (53.6%)	8/23 (34.8%)	1.54 (0.80-2.97)
Bronchiectatic segments			
<10	18/47 (38.3%)	24/61 (39.3%)	0.97 (0.60-1.57)
≥10	28/47 (59.6%)	14/36 (38.9%)	1.53 (0.96-2.46)
High-attenuation mucus			
No	26/55 (47.3%)	23/58 (39.7%)	1.19 (0.78-1.82)
Yes	20/39 (51.3%)	15/39 (38.5%)	1.33 (0.81-2.20)
All participants	31/94 (33.0%)	20/97 (20.6%)	1.60 (0.98-2.60)