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

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Shareable abstract (@ERSpublications)
Combination therapy with prednisolone–itraconazole resulted in a nonsignificant decline in the occurrence of ABPA exacerbations at 1 year compared with prednisolone monotherapy in acute-stage ABPA complicating asthma https://bit.ly/2Yna4Lp

Cite this article as: Agarwal R, Muthu V, Sehgal IS, *et al*. A randomised trial of prednisolone *versus* prednisolone and itraconazole in acute-stage allergic bronchopulmonary aspergillosis complicating asthma. *Eur Respir J* 2022; 59: 2101787 [DOI: 10.1183/13993003.01787-2021].

Received: 24 June 2021
Accepted: 29 Aug 2021

Abstract

Background 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.

Methods We randomised subjects with treatment-naïve acute-stage ABPA complicating asthma to receive either prednisolone alone (4 months) or a combination of prednisolone and itraconazole (4 and 6 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, percentage decline in serum total IgE at 6 weeks, time to first ABPA exacerbation and treatment-emergent adverse events (TEAEs).

Results We randomised 191 subjects to receive either prednisolone (n=94) or prednisolone–itraconazole combination (n=97). The 1-year exacerbation rate was 33% and 20.6% in the prednisolone monotherapy and prednisolone–itraconazole combination arms, respectively (p=0.054). None of the participants progressed to glucocorticoid-dependent ABPA. All of the subjects experienced a composite response at 6 weeks, along with a decline in serum total IgE (mean decline 47.6% *versus* 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 TEAEs.

Conclusions There was a trend towards a decline in ABPA exacerbations at 1 year with the prednisolone–itraconazole combination *versus* 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.

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 haemoptysis [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 hypothesised 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 randomised controlled trial (RCT) 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 RCT involving subjects with ABPA attending the Chest Clinic of the Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, India. The Institute Ethics Committee approved the study protocol (NK/2047/Res/521; supplementary material) and written consent was obtained from all subjects before enrolment. The study protocol is registered at ClinicalTrials.gov (NCT02440009). Results are reported according to the CONSORT (Consolidated Standards of Reporting Trials) statement.

Inclusion criteria

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

Exclusion criteria

We excluded subjects with any of the following: intake of systemic glucocorticoids or triazoles for >3 weeks in the preceding 6 months; concomitant use of medications, including voriconazole, inhaled amphotericin B, omalizumab or other biological agents; enrolment in another trial of ABPA; uncontrolled diabetes mellitus, chronic renal failure, chronic liver failure or immunosuppressive drugs; pregnancy; and 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 (as a single morning dose) sequentially at 0.5, 0.25 and 0.125 $mg \cdot kg^{-1}$ per day for 4 weeks each. The drug was then tapered by 5 mg every 2 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 6 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 corticosteroid, long-acting β_2-agonist (formoterol) and leukotriene receptor antagonist (montelukast) in both the groups, at the discretion of the treating physician.

Outcomes

The primary outcomes were: relapse (exacerbation) rates within 12 months and progression to glucocorticoid-dependent ABPA within 24 months after treatment initiation. The secondary outcomes were: proportion of subjects with a composite response (as defined in the Definitions section) after 6 weeks of treatment, percentage decline in serum total IgE (baseline IgE minus IgE after 6 weeks/baseline IgE) at 6 weeks of treatment, time to first ABPA exacerbation and treatment-emergent adverse events (TEAEs).

Study procedure

Data were collected in case record forms, entered in a computerised data gathering platform (Epicollect 5; https://five.epicollect.net) and validated against the record books before analysis. We collected the following information at baseline: clinical details (age, sex, duration of asthma, history of haemoptysis, expectoration of brownish-black mucus plugs and others); immunological test results (serum total IgE, *A. fumigatus*-specific IgE and IgG, *A. fumigatus* precipitins, and peripheral blood eosinophil count); spirometry (forced expiratory volume in 1 s (FEV_1) and forced vital capacity (FVC)); and chest radiography and chest CT findings. We observed the subjects every 6 weeks for 6 months and then every 6 months or earlier if there were worsening symptoms. We monitored the clinical status, chest radiography 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, hyperglycaemia, 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 determined serum total IgE, and *A. fumigatus*-specific IgE and IgG, using a commercially available fluorescent enzyme immunoassay (Phadia 100; Thermo Fisher Scientific, Uppsala, Sweden), as previously described [8]. Serum precipitins were determined using the Ouchterlony double-gel diffusion method [9, 10].

Definitions

We documented clinical improvement in cough and dyspnoea 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) and 4=significant improvement (>75% of baseline). We classified treatment effects as: composite response (defined as an improvement in cough and dyspnoea (>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 6 weeks of treatment), ABPA relapse (exacerbation) (doubling of 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), glucocorticoid-dependent ABPA (if the patient relapsed on two or more consecutive occasions within 6 months of stopping treatment or required oral glucocorticoids for asthma control) or asthma exacerbation (worsening of cough or dyspnoea in the absence of immunological or radiological deterioration of ABPA).

Treatment of asthma, asthma exacerbations and ABPA relapses (exacerbations) during follow-up

After initial randomisation and completion of the treatment as per the trial allocation, we managed the patients as follows. We treated the first ABPA exacerbation with oral prednisolone at the aforementioned doses. The subsequent exacerbations were managed with a combination of oral prednisolone and itraconazole at the aforementioned doses. We used voriconazole in subjects intolerant to itraconazole. We used inhaled formoterol/fluticasone (6/125 µg, as a single inhaler) one puff twice daily and as-needed for asthma management. Asthma exacerbations were managed with oral prednisolone (0.5 $mg \cdot kg^{-1}$ per day) for 7 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 10% compared with the prednisolone group. In the largest dataset available, the exacerbation rate in ABPA was ∼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 assumed 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 randomisation of 190 subjects.

Randomisation

We randomly assigned study participants in a 1:1 ratio to receive either prednisolone alone or a combination of prednisolone and itraconazole. The randomisation 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

Data were analysed on an intention-to-treat basis. We used the statistical packages SPSS version 21 (IBM, Armonk, NY, USA), StatsDirect version 3.3 (StatsDirect, Birkenhead, UK) and MedCalc version 20.0.7 (MedCalc, Ostend, Belgium) to perform the statistical analysis. Data are presented as mean with standard deviation or 95% confidence interval, median (interquartile range (IQR)) or number (percentage). We compared categorical and continuous variables using the Chi-squared test (or Fisher's exact test) and t-test (or Mann–Whitney U-test), respectively. We analysed time to first exacerbation using 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 1 and 2 years of treatment initiation. Statistical significance was assumed at $p<0.05$. All p-values are two-sided and are presented without adjustment for multiple testing.

Results

Baseline characteristics

We screened 325 subjects with ABPA between May 2014 and July 2017 (figure 1). Of these, we randomised 191 to receive either prednisolone alone (n=94) or prednisolone–itraconazole combination

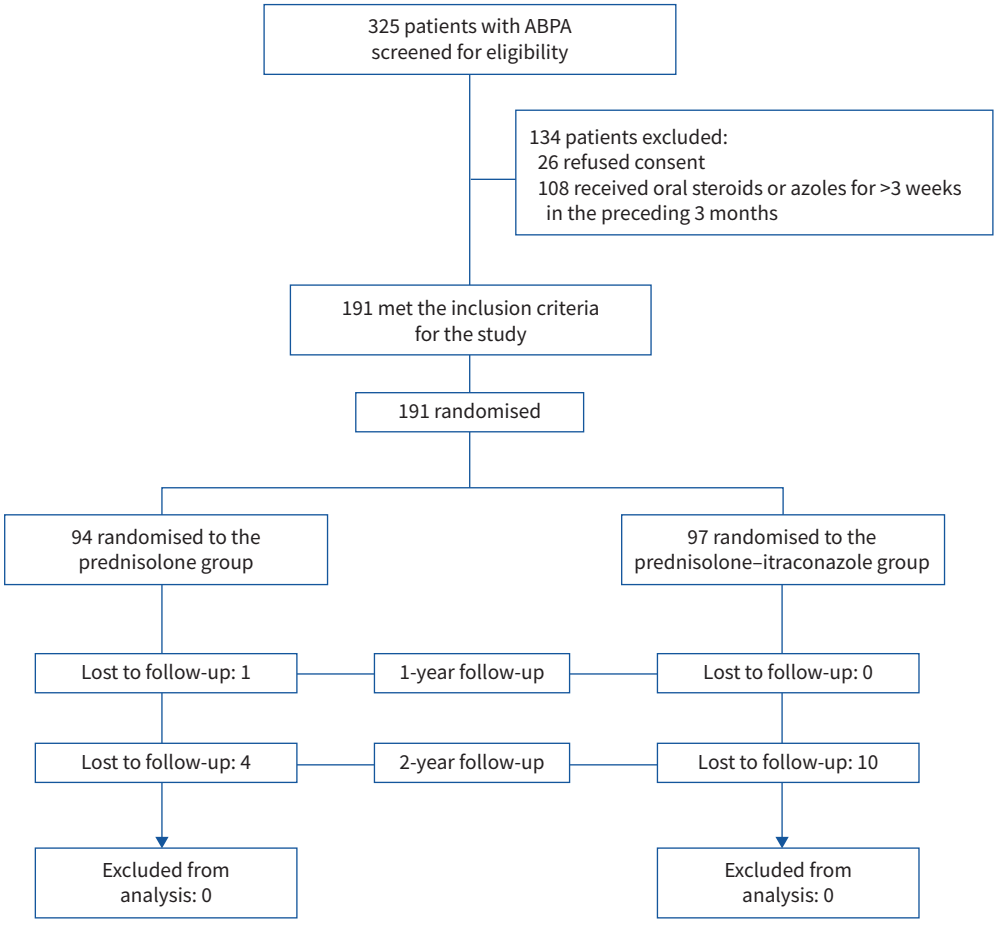

FIGURE 1 CONSORT diagram depicting the flow of participants in the study. ABPA: allergic bronchopulmonary aspergillosis.

(n=97). All of the randomised subjects received the intended treatment and the majority completed 1 year of follow-up; 14 patients were lost to follow-up at 2 years (figure 1). The mean±SD 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 enrolment in the study. The baseline clinical characteristics were similar in both study groups, except for lower mean body weight in the prednisolone monotherapy arm compared with the combination arm (53.1 *versus* 57 kg, respectively; p=0.04). We encountered an abnormal chest radiograph or CT scan in 68.6% and 97.4% of the participants, respectively. Bronchiectasis was the most common abnormality on chest CT (n=180 (94.2%)) 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 β_2-agonists, while 38% also received montelukast. The dose of inhaled corticosteroid 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 2 years of follow-up.

Primary outcomes

The proportion of subjects experiencing ABPA exacerbations within 1 year of treatment initiation was 33.0% and 20.6% in the prednisolone monotherapy and prednisolone–itraconazole combination groups, respectively (p=0.054). None of the study subjects progressed to glucocorticoid-dependent ABPA within 2 years of treatment initiation. 84 subjects experienced ABPA exacerbations at 2 years of completing initial treatment and the proportion was not different between the study groups (48.9% *versus* 39.2%; p=0.17).

TABLE 1 Baseline characteristics of the study population (n=191)

	Prednisolone (n=94)	Prednisolone–itraconazole (n=97)
Demographic variables		
Age, years	34.1±12.4	36.2±12.4
Female	57 (60.6)	51 (52.6)
Height, cm	161.0±9.4	162.4±9.5
Weight*, kg	53.1±11.4	57±13.6
Duration of asthma, years	11.8±9.4	13.8±9.6
Haemoptysis	30 (31.9)	32 (33.0)
Brownish-black mucus plugs	16 (1.07)	18 (18.6)
Spirometry		
FEV_1, L	1.73±0.69	1.78±0.80
FVC, L	2.55±0.81	2.62±0.87
FEV_1/FVC, %	66.0±14.8	65.0±12.8
Severity of obstruction		
Normal (FEV_1 >80% pred)	23 (24.5)	22 (22.7)
Mild obstruction (FEV_1 60–80% pred)	34 (36.2)	29 (29.9)
Moderate obstruction (FEV_1 40–60% pred)	21 (22.8)	31 (32.0)
Severe obstruction (FEV_1 <40% pred)	14 (15.2)	15 (15.5)
Chest radiography findings		
Any abnormality	61 (64.9)	70 (72.2)
Fleeting opacities	39 (41.5)	47 (48.5)
Chest CT findings		
Normal HRCT (serological ABPA)	2 (2.1)	3 (3.1)
Bronchiectasis	88 (93.6)	92 (94.8)
High-attenuation mucus	39 (41.5)	39 (40.2)
Mean (IQR) bronchiectatic segments, n	10 (5.8–13)	8 (5–11)
Immunological findings		
Aspergillus skin test	83/91 (91.2)	85/95 (89.5)
Mean (95% CI) *A. fumigatus*-specific IgE, $kU_A \cdot L^{-1}$	37.7 (31.8–43.6)	35.1 (30.0–40.2)
Mean (95% CI) *A. fumigatus*-specific IgG, $mg_A \cdot L^{-1}$	95.0 (82.1–107.9)	84.4 (72.2–96.6)
Mean (95% CI) total IgE, $IU \cdot mL^{-1}$	10 221 (8800–11 642)	8950 (7461–10 440)
Mean (95% CI) total eosinophil count, μL^{-1}	1337 (1064–1610)	1106 (863–1350)
Aspergillus precipitins	37/89 (41.6)	29/96 (30.2)
Sputum cultures		
A. fumigatus	12 (12.8)	8 (8.2)
A. flavus	16 (1.07)	15 (15.5)
No growth	18 (19.2)	20 (20.6)
No sputum	48 (51.1)	54 (55.7)
Asthma treatment		
Subjects on ICS	94 (100)	97 (100)
Dose of ICS (BDPE), µg per day	416±269	368±229
Subjects on LABA	94 (100)	97 (100)
Dose of formoterol, µg per day	13.9±6.2	14.5±6.5
Subjects on montelukast	33 (35.1)	39 (40.2)

Data are presented as mean±SD, n (%) or n/N (%), unless otherwise stated. FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; (HR)CT: (high-resolution) computed tomography; ABPA: allergic bronchopulmonary aspergillosis; IQR: interquartile range; *A. fumigatus*: *Aspergillus fumigatus*; *A. flavus*: *Aspergillus flavus*; ICS: inhaled corticosteroids; BDPE: beclomethasone dipropionate equivalent; LABA: long-acting β_2-agonist. *: p<0.05.

Secondary outcomes

All of the study participants in both study groups satisfied the criteria for a composite response at 6 weeks of treatment (table 2). The decline in serum total IgE at 6 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=0.43, log-rank test) between the study groups (figure 2). FEV_1 improved by ∼300 mL in each group; however, the improvement was not statistically different between the two study groups (table 2).

Treatment-emergent adverse events

We detected TEAEs in 78.7% and 73.2% of the subjects in the prednisolone monotherapy and prednisolone–itraconazole combination groups, respectively (p=0.37). The proportion of subjects

TABLE 2 Outcomes of the study subjects (n=191) treated with prednisolone or prednisolone–itraconazole

	Prednisolone (n=94)	Prednisolone–itraconazole (n=97)	Estimate difference (95% CI)	p-value
Primary outcomes				
Subjects experiencing exacerbation after 1 year	31 (33.0)	20 (20.6)	12.3 (−0.2–24.5)	0.054
Subjects experiencing glucocorticoid-dependent ABPA after 2 years	0	0		
Secondary outcomes				
Response after 6 weeks of treatment	94 (100)	97 (100)	0 (−0.04–0.04)	1.0
Decline in IgE after 6 weeks of treatment, %	47.6 (43.3–51.9)	45.6 (41.0–50.1)	2.0 (−4.2–8.2)	0.47
Mean time to first exacerbation, days	416.2 (371–461)	417.7 (365–470)	−1.5 (−45.3–42.3)	0.84
TEAEs				
Any TEAE	74 (78.7)	71 (73.2)	5.5 (−6.6–17.4)	0.37
Cushingoid facies	70 (74.5)	70 (72.2)	2.3 (−10.2–14.7)	0.19
Weight gain	37 (39.3)	36 (37.1)	2.2 (−11.3–15.8)	0.86
Deranged liver functions	6 (6.2)	21 (21.6)	15.4 (5.5–25.1)	0.001
Hypertension	2 (2.1)	1 (1.0)	1.1 (−3.7–6.5)	1.0
Hyperglycaemia	2 (2.1)	0	2.1 (−2.0–7.4)	0.50
Hirsutism	2 (2.1)	3 (3.1)	−1.0 (−6.8–4.7)	0.68
Emotional lability	1 (1.1)	1 (1.0)	0.1 (−4.6–4.8)	1.0
Other outcomes				
Spirometry				
Difference in FEV_1 after 6 weeks of treatment, mL	341 (286–396)	324 (268–380)	17 (−60–94)	0.67
Difference in FVC after 6 weeks of treatment, mL	361 (305–417)	342 (281–403)	19 (−63–101)	0.65
ABPA exacerbations				
1 year	0.58 (0.45–0.72)	0.43 (0.29–0.58)	0.15 (0.01–0.29)	0.14
2 years	1.09 (0.92–1.27)	0.96 (0.79–1.12)	0.13 (−0.04–0.3)	0.29
Total asthma exacerbations after 2 years	0.79 (0.61–0.97)	0.61 (0.44–0.77)	0.18 (−0.06–0.42)	0.14

Data are presented as n (%), n or mean (95% CI), unless otherwise stated. ABPA: allergic bronchopulmonary aspergillosis; TEAE: treatment-emergent adverse event; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

experiencing various TEAEs related to prednisolone was similar in both study groups (table 2). Deranged liver function tests were significantly more common in subjects receiving combination therapy compared with monotherapy (21.6% *versus* 6.2%; p=0.001). However, no subject required discontinuation of therapy due to TEAEs.

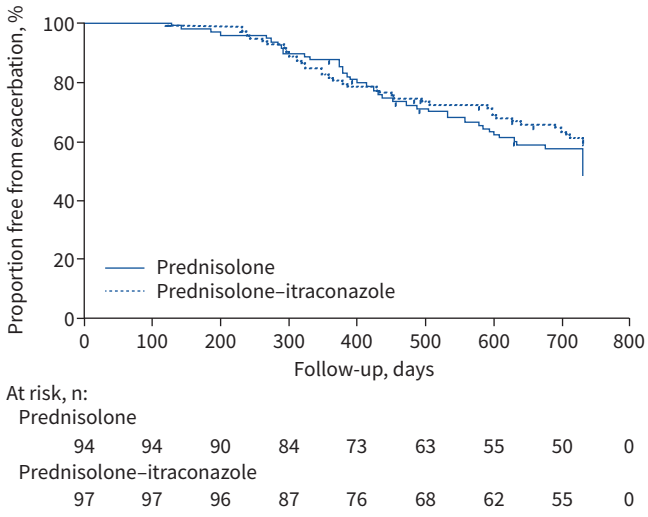

FIGURE 2 Kaplan–Meier curve demonstrating the probability of exacerbation against the duration of follow-up. The mean time to first allergic bronchopulmonary aspergillosis (ABPA) exacerbation was 417 days and was not statistically different (p=0.43, log-rank test) between the study groups.

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 (supplementary figure S1) after treatment initiation. We found peripheral blood eosinophil count ⩾1000 cells·μL^{-1}, extensive bronchiectasis (⩾10 segments) and absence of high-attenuation mucus to be associated with a lower exacerbation rate at 1 year using combination therapy. The exacerbation rate at 2 years (supplementary figure S1) in the combination therapy arm was significantly lower *versus* prednisolone alone in the subgroup of patients with peripheral blood eosinophilia (⩾1000 cells·μL^{-1}) and raised *A. fumigatus*-specific IgG values (⩾100 mg$_A$·L^{-1}). We discerned no relationship between combination therapy and spirometric (FEV_1 % pred) and other immunological (serum total IgE and *A. fumigatus*-specific IgE), microbiological or imaging findings on exacerbation rate at 2 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 combination therapy decreases the exacerbation rate by >10% as opposed to prednisolone monotherapy. The response rates and the decline in IgE values after 6 weeks were similar in the two groups. While TEAEs were similar in both groups, asymptomatic transaminitis was higher in the prednisolone–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 guidelines suggest combination therapy in the treatment of ABPA [12]. Nevertheless, 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 randomised [13]. To the best of our knowledge, the current study is the first RCT on combination therapy in ABPA.

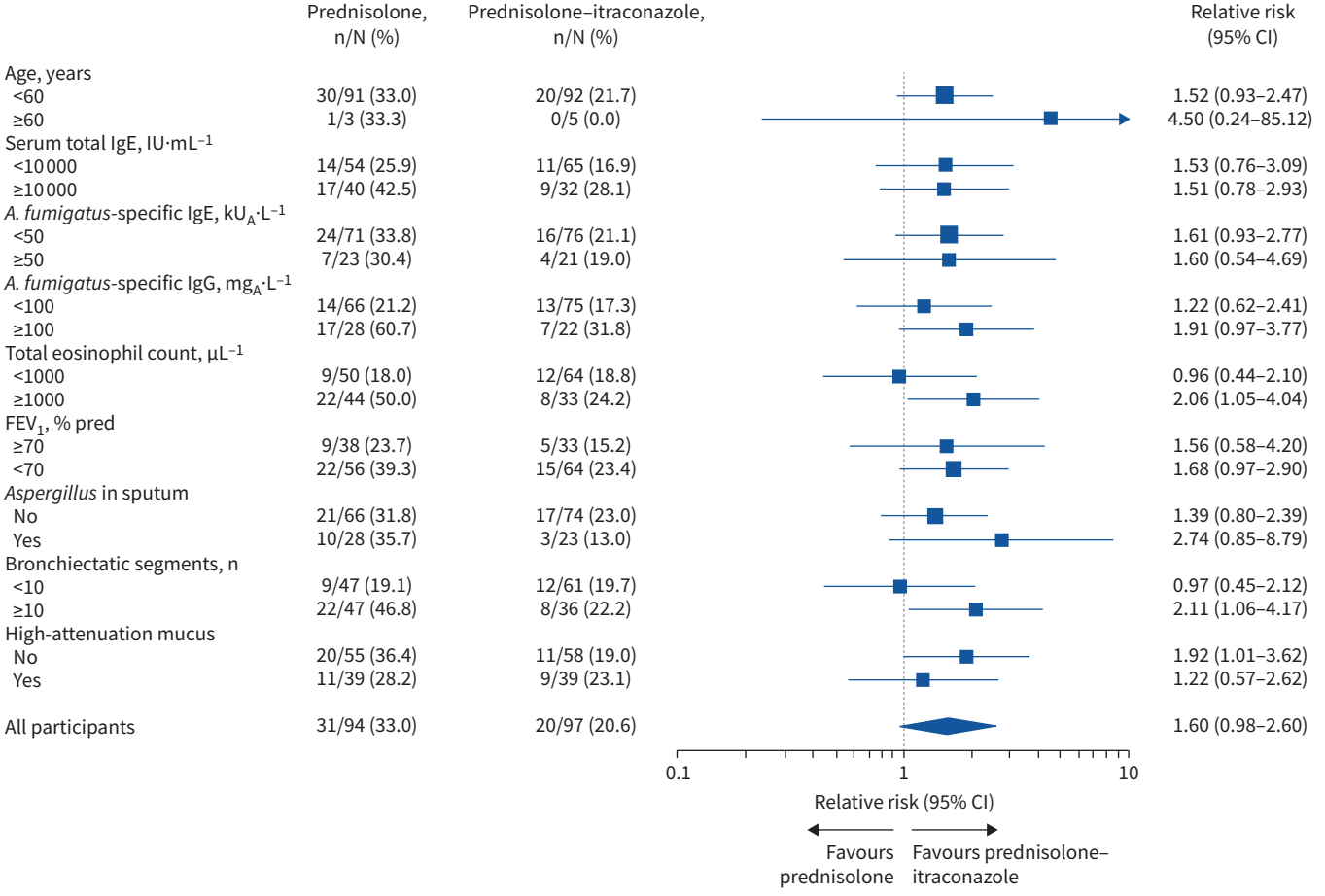

FIGURE 3 Effect of allocation to prednisolone–itraconazole combination *versus* prednisolone alone on 1-year exacerbation rate in a *post hoc* analysis of various subgroups. *A. fumigatus*: *Aspergillus fumigatus*; FEV_1: forced expiratory volume in 1 s.

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 6 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 favour of the combination arm could also be explained by the fact that itraconazole is a potent cytochrome P450 3A4 (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 2 years possibly indicates the limited period of action of azole therapy with subsequent recolonisation 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 a primary end-point.

Only a few randomised 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 $mg \cdot kg^{-1}$ per day) was found to be as effective as a higher dose (8–10 month course with oral prednisolone starting at 0.75 $mg \cdot kg^{-1}$ per day) in preventing exacerbations after 1 and 2 years, with lesser side-effects. However, the response rates at 6 weeks were lower in the low-dose arm (88% *versus* 100%) [17]. Another RCT found itraconazole (200 mg twice daily for 4 months) to be associated with a lower response rate (88% *versus* 100%) at 6 weeks compared with oral prednisolone for 4 months (with an initial dose of 0.5 $mg \cdot kg^{-1}$ per day). After excluding the early failures, exacerbations after 1 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 6 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 with treatment-naïve acute-stage ABPA treated with prednisolone–itraconazole combination may have a lower exacerbation frequency at 1 year than with prednisolone monotherapy. Furthermore, the combination therapy was beneficial in specific subgroups (patients with peripheral blood eosinophil count $\geqslant$1000 $cells \cdot \mu L^{-1}$ and those with bronchiectasis involving $\geqslant$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 of 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 nonresponders or in the aforementioned specific subgroups. This treatment approach would maximise 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-centre study with ABPA patients at the most severe end of the spectrum characterised 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 to 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 nonsignificant reduction in ABPA exacerbations at 1 year compared with prednisolone monotherapy. Larger studies are required to validate our findings.

This study is registered at ClinicalTrials.gov with identifier number NCT02440009. Data will be made available on request to the corresponding author.

Conflict of interest: R. Agarwal has received grant support for conducting research in ABPA from Cipla Pharmaceuticals, Mumbai, India, outside the submitted work. V. Muthu has nothing to disclose. I.S. Sehgal has nothing to disclose. S. Dhooria has nothing to disclose. K.T. Prasad has nothing to disclose. M. Garg has nothing to disclose. A.N. Aggarwal has nothing to disclose. A. Chakrabarti has nothing to disclose.

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