Original Article

Treating Allergic Bronchopulmonary Aspergillosis with Short-Term Prednisone and Itraconazole in Cystic Fibrosis

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What is already known about this topic? Allergic bronchopulmonary aspergillosis (ABPA) contributes significantly to cystic fibrosis (CF) lung disease. The optimal treatment strategy, however, is yet to be defined.

What does this article add to our knowledge? The combination of short-term prednisone and long-term itraconazole treatment is effective in preventing ABPA-induced lung function decline without detrimental glucocorticoid side effects in patients with CF.

How does this study impact current management guidelines? The proposed regimen offers a new approach to treat CF-related ABPA reducing both lung function deterioration and glucocorticoid-induced adverse effects. It might, therefore, help optimizing current treatment guidelines.

BACKGROUND: Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity reaction to *Aspergillus fumigatus* contributing to cystic fibrosis (CF) lung disease.
OBJECTIVE: To evaluate the combination of oral prednisone for 18 days together with itraconazole therapy for at least 12 months in CF-related ABPA with regard to long-term pulmonary function and side effects.
METHODS: Sixty-five patients with CF treated for ABPA and 127 patients with CF without ABPA serving as matched controls were retrospectively analyzed for a median period of 4.8 years. Serial lung functions were analyzed alongside clinical, microbiological, and laboratory data including itraconazole therapeutic drug monitoring.
RESULTS: The used ABPA treatment regimen restored FEV_1 values to pre-ABPA levels within 3 months ($P < .0001$). Long-term FEV_1 courses of patients showed no difference when compared with those of ABPA-free controls. Glucocorticoid treatment was not associated with increased CF-related diabetes incidence, growth restriction, or *Pseudomonas aeruginosa* acquisition. Patients who experienced ABPA relapses displayed lower itraconazole trough levels during the first 3 months of treatment ($P < .05$). A decreased risk of ABPA recurrence was further associated with *P aeruginosa* colonization.
CONCLUSIONS: The proposed treatment scheme for CF-related ABPA is effective in preserving lung function capacity over years in affected individuals without the known glucocorticoid-associated side effects. Itraconazole therapeutic drug monitoring seems useful to prevent disease flares, for which *P aeruginosa*—negative patients with CF might be particularly susceptible. © 2020 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2020;■:■-■)

Key words: *Cystic fibrosis; ABPA;* Aspergillus fumigatus*; Itraconazole; TDM;* Pseudomonas aeruginosa*; Lung function; IgE*

INTRODUCTION

Cystic fibrosis (CF) is caused by mutations in the cystic fibrosis transmembrane conductance regulator gene encoding a chloride and bicarbonate transport channel that maintains osmotic balance across body surfaces.[1] Progressive lung disease is the major determinant of life span and quality of life in affected individuals.[2] The reduced transport of chloride and accompanying water across the airway epithelium compromises both mucociliary clearance and antibacterial activity and renders patients susceptible to various opportunistic pathogens.[1] Pulmonary morbidity is largely influenced by chronic infection with *Pseudomonas aeruginosa*, whereas the contribution of fungi is less clear.[3,4] Allergic bronchopulmonary aspergillosis (ABPA) is a hypersensitivity disorder directed against the environmental fungus *Aspergillus fumigatus*, present in about 10% of pediatric and adult patients with CF.[5] ABPA often shows a relapsing course, with frequent exacerbations eventually leading to bronchiectasis and pulmonary fibrosis.[6] Its diagnosis remains

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Abbreviations used
ABPA- allergic bronchopulmonary aspergillosis
AUC- area under the curve
CF- cystic fibrosis
CFRD- cystic fibrosis–related diabetes
IQR- interquartile range
TDM- therapeutic drug monitoring

challenging because symptoms are often hard to distinguish from bacterial lung infections commonly affecting patients with CF. High and especially rising total IgE levels, the detection of *A fumigatus*–specific IgE and IgG, positive sputum galactomannan and *A fumigatus* PCR results, as well as basophil activation can aid clinical decision making because a diagnostic gold standard is lacking.[7-9] Current treatment strategies reflect the complicated role ABPA plays at the crossroads of infection and allergy. The administration of systemic glucocorticoids is the first-line treatment to suppress acute inflammatory responses and resolve obstructive lung function decline, but their use is of special concern in patients with CF already prone to diabetes, osteopenia, and stunting of growth.[10,11] Anti-infective treatment with itraconazole is thought to reduce fungal burden in the airways, thereby limiting antigenic stimulation.[12] However, controlled trials in patients with CF are lacking for both drugs, leaving the questions of optimal dosing and treatment duration unanswered.[13,14] Hence, there is still work to be done to find the right balance between controlling acute allergic reactions and minimizing adverse treatment effects.

The present case-control study evaluates the effectiveness and side effects of a combined prednisone and itraconazole treatment regimen for CF-related ABPA.

METHODS

Study design

This investigator-initiated, retrospective case-control study was performed on patients treated between January 2007 and December 2016 in the Cystic Fibrosis Center at the Dr von Hauner Children's Hospital in Munich, Germany. The study was approved by the research ethics board of the Ludwig-Maximilians University (EK 16/5/2008).

Subjects

CF diagnosis was confirmed by the typical phenotype, a pathologic sweat test result, and the detection of 2 deleterious variants in the cystic fibrosis transmembrane conductance regulator gene. Patients were followed every 3 months in our outpatient service. These regular visits included lung function measurements, respiratory tract specimen culture, and a blood draw. Only in children younger than 10 years, blood was taken semiannually. Lung function measurements started between age 4 and 6 years, and pediatric reference values were obtained from Zapletal and Samanek.[15] In adults, normal ranges reported by Quanjer et al were used.[16] To assess long-term lung function, the best FEV_1 value (% predicted) within 6 months before ABPA treatment onset was compared with the best value obtained during individual follow-up years. Only patients followed for longer than 1 year were considered for these analyses. Body weight, height, and body mass index were obtained at first ABPA treatment and the end of follow-up period, with percentiles calculated according to Hemmelmann et al[17] in adults and Rosario et al[18] in children.

Matching

Two sex-matched CF controls without ABPA were assigned per ABPA case. Regarding age, differences of less than 1 year in patients younger than 18 years and less than 2 years in adults were sought. Discrepancies in FEV_1 levels within 6 months before ABPA onset were less than 10% in most cases. We further aimed to match cases and controls regarding *P aeruginosa* status comparing all microbiology test results taken in the 12 months before ABPA treatment. In addition, most controls had undetectable specific IgE against *A fumigatus*, confirming *A fumigatus* naivety. Earlier exposure to itraconazole treatment was also recorded and matched when possible. Details of the matching quality are presented in Table I.

ABPA diagnosis

The diagnosis of ABPA was established as previously described.[7] Worsening of clinical status, obstructive deterioration of lung function, rising total IgE levels, failure of treatment with antibiotics, appearance of new shallow infiltrates on chest x-ray, and the presence of specific IgE against *A fumigatus* were taken into account.

Itraconazole therapeutic drug monitoring

Serum trough levels of itraconazole were measured routinely in the Institute of Laboratory Medicine at the University Hospital LMU, Munich, Germany, in a validated LC-MS assay. The lower detection limit of the assay was 20 μg/L, and this value was used for analysis when levels were reported "undetectable." For the analysis of itraconazole levels over time, measurements were assigned to 3-month intervals posttreatment initiation. If more than 1 therapeutic drug monitoring (TDM) level was available in a given interval, then the mean value was used.

Assessment of treatment side effects

Glycated hemoglobin A1c levels and liver transaminases were monitored routinely. Patients were considered *P aeruginosa*–colonized/infected if 1 microbiological specimen was positive within the last 12 months.

Statistics

Data were analyzed using GraphPad Prism 8.3 (GraphPad Software, San Diego, Calif) and are shown as median plus interquartile range (IQR) unless otherwise indicated. Different groups were compared using Mann-Whitney *U* test or ANOVA/Kruskal-Wallis test with Dunn post hoc testing. Kaplan-Meier analysis was applied to study the time until first ABPA relapse. Itraconazole levels were compared using *t* tests of the log-transformed values as well as area under the curve (AUC) calculations. A multiple logistic regression model was used to evaluate risk factors for ABPA recurrence. *P* values of less than .05 were considered statistically significant.

RESULTS

Study cohort

ABPA was diagnosed in 65 patients (48% male) between January 2007 and December 2016. For every case, 2 controls were assigned (n = 127) on the basis of the criteria mentioned earlier. Baseline characteristics of the study population are presented in Table I. The median age at first ABPA diagnosis was 13.5 years (IQR, 10.3-23.3).

TABLE I. Clinical characteristics of patients with ABPA and controls at baseline (ie, the time of matching pre-ABPA onset)

Clinical characteristics	Patients (n = 65)	Controls (n = 127)	*P* value	Matching
Age (y)	13.5 (10.3 to 23.3)	13.2 (9.9 to 20.9)	.83	0.1 (−0.6 to 1)
Sex: male	31 (48%)	59 (47%)	.65	100%
F508del homozygous	33 of 65 (51%)	66 of 127 (52%)	.88	
F508del heterozygous	20 of 65 (31%)	44 of 127 (35%)	.63	
FEV_1 (% predicted)	98.1 (84.1 to 108.3)	100.5 (81.2 to 110.1)	.93	−0.5 (−6.3 to 5.1)
BMI percentile	39 (18 to 67)	44 (23 to 66)	.50	
CFRD prevalence	5 of 65 (6%)	4 of 127 (3%)	.28	
Chronic *P aeruginosa*	18 of 65 (28%)	56 of 127 (44%)	.16	67%
A fumigatus−RAST-positive	32 of 65 (49%)	11 of 127 (9%)	**<.0001**	

Note. Data are displayed as either frequencies or median + IQR. Bold text indicates statistical significance.
BMI, Body mass index; *RAST*, radioallergosorbent test.

The ABPA treatment scheme evaluated in this study combined short-term glucocorticoid with long-term itraconazole treatment. Prednisone was used at a starting dose of 2 mg/kg body weight for 3 days before being tapered every 5 days to 1, 0.5, and 0.25 mg/kg body weight and discontinued after 18 days in total. Itraconazole was commenced at a daily dose of 10 mg/kg body weight for capsules and 5 mg/kg body weight for suspension (in 18% of cases) from day 1 of treatment and continued for at least 12 months (Figure 1). Altogether, 106 ABPA treatment courses were identified. The episodes preceding treatment were characterized by a median total IgE increase of 146% within 3 months (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).

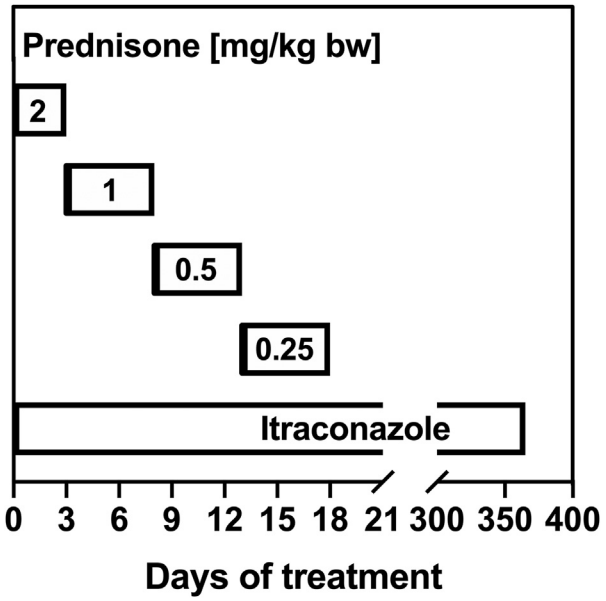

FIGURE 1. ABPA treatment regimen. Prednisone dosing in milligram per kilogram of body weight and tapering scheme as indicated. Itraconazole was commenced at a starting dose of 10 mg/kg bw for capsules or 5 mg/kg bw for suspension. Following TDM measurements, doses were adjusted to meet a target concentration of 500-1000 μg/L. Two episodes were treated with posaconazole in our cohort. *bw*, Body weight.

Lung function recovery within 12 months after ABPA diagnosis

To see whether the aforementioned treatment scheme was capable of restoring lung function, FEV_1 values were assessed pretreatment and in 3-month intervals during the first year posttreatment (Figure 2). At ABPA diagnosis and treatment initiation, the median FEV_1 decline was 25% ($P < .0001$; see Table E1 in this article's Online Repository). After 3 months of treatment, FEV_1 levels showed substantial recovery although not fully reaching pre-ABPA levels ($P < .0001$). At this point, patients had already been weaned off prednisone for more than 2 months and lung function remained stable with itraconazole until the end of the first follow-up year.

Long-term pulmonary outcome and treatment side effects

Next, we asked how ABPA treatment might impact long-term pulmonary function. Patients and their respective controls were followed together for a median of 4.8 years (IQR, 2.3-6.5). When comparing the best FEV_1 values obtained in the respective follow-up years, we could not observe any difference between patients and controls (Figure 3; see also Figure E1 in this article's Online Repository at www.jaci-inpractice.org). In addition, we assessed the potential side effects of glucocorticoid treatment. There was no significant difference between patients and controls in the rate of acquired *P aeruginosa* infection/colonization (17/47 vs 18/71; $P = .22$; see Table II). However, the *P aeruginosa* colonization rate at ABPA diagnosis was substantially lower in patients than in controls (18 of 56 vs 56 of 127; $P = .16$), an effect even more pronounced when looking at pediatric patients (4 of 42 vs 21 of 83; $P = .06$) or male patients only (6 of 31 vs 27 of 59; $P = .02$; see Table E2 in this article's Online Repository at www.jaci-inpractice.org). During the follow-up period, *P aeruginosa* acquisition rates were generally higher in patients; however, they did not reach statistical significance (see Table E2). At the end of the follow-up period, *P aeruginosa* positivity rates were similar (35 of 65 vs 74 of 127; $P = .65$; Table II). The prevalence of CF-related diabetes (CFRD) at baseline was slightly higher in the patients (5 of 65 vs 4 of 127; $P = .28$), whereas the incidence of CFRD during follow-up was again comparable in both groups (7 of 65 vs 12 of 127; $P = .77$; Table II; see also Table E2). Median body height percentiles in pediatric patients at the end of the follow-up period were nearly identical (25.0 vs 22.5; $P = .94$), suggesting there was no glucocorticoid-induced growth restriction (Table II).

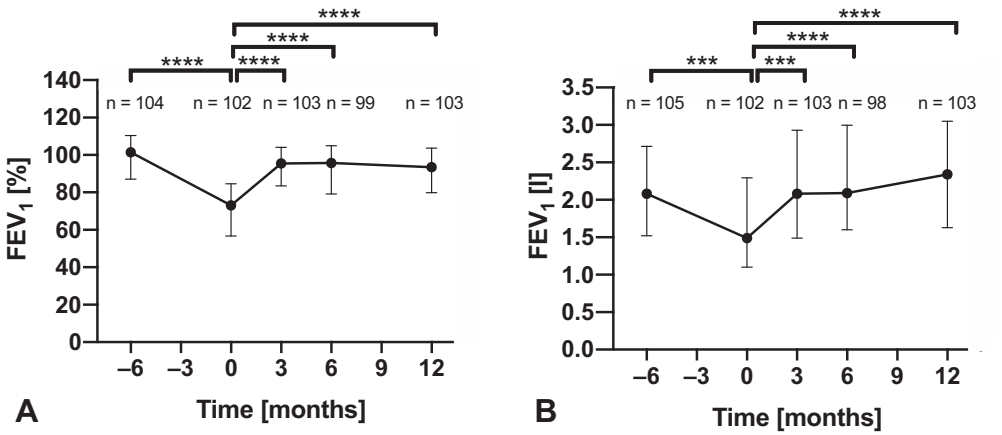

FIGURE 2. Lung function recovery in the first year after ABPA diagnosis. (**A**) FEV_1 in % predicted, (**B**) absolute values in liters. Symbols indicate median + IQR. Numbers represent the number of lung function measurements available for analysis at each time point. ***$P <$ .001, ****$P <$ .0001.

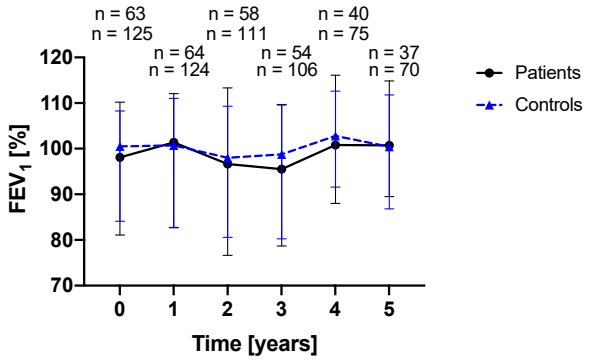

FIGURE 3. Long-term FEV_1 course in patients and controls. The best FEV_1 values obtained in individual follow-up years were compared in patients (black circle) and controls (blue triangle). Symbols represent median ± IQR. Numbers indicate patients (top) and controls (bottom) followed at respective time points.

Itraconazole-related gastrointestinal side effects led to treatment discontinuation in 1 individual, and 1 episode of transient transaminitis was found to be potentially azole-related.

ABPA relapses and itraconazole TDM

One-third of patients (22 of 65) displayed an ABPA relapse requiring at least 1 further treatment course (Figure 4; see also Figure E2 in this article's Online Repository at www.jaci-inpractice.org). Twelve of these 22 patients experienced their first relapse within 18 months of the initial diagnosis. To understand which factors might predispose patients to ABPA recurrence, we analyzed 794 itraconazole serum trough levels (median, 5; IQR, 2-11 measurements per individual). Although itraconazole AUC levels differed neither in the first 12 months after treatment initiation ($P = .64$) nor after 36 months between no-relapse and relapse patients ($P = .42$), we noted significantly lower median itraconazole serum trough levels in the relapse group during the first 3 months of treatment (544 mg/L [IQR, 115-809] in relapse patients vs 881 mg/L [IQR, 497-1295] in non-relapse patients [$P = .04$; Figure 5]). Additional significant differences between the 2 groups were also present in months 9 to 12 (577 mg/L [IQR, 275-1220] in relapse patients vs 244 mg/L [IQR, 77-550] in non-relapse patients [$P = .048$]).

We wondered whether we could identify risk factors for ABPA recurrence also including the detection of *A fumigatus*, *P aeruginosa*, or *Candida albicans* in microbiological specimen as well as the presence of specific IgE against *A fumigatus* using a multiple logistic regression model (Table III). Here, we identified a significant impact of itraconazole levels during the first 3 months of treatment (adjusted odds ratio, 0.14; adjusted 95% CI, 0.02-0.68; $P = .03$). We were further surprised to note that colonization with *P aeruginosa* might be associated with a lower risk for ABPA recurrence (adjusted odds ratio, 0.04; adjusted 95% CI, 0.003-0.37; $P = .01$). Interestingly, 66% of all ABPA treatment courses (70 of 106) were administered to patients considered *P aeruginosa*—negative at the time.

DISCUSSION

The present study shows a favorable long-term pulmonary outcome in patients with ABPA treated with a combination of short-term prednisone and itraconazole.

The treatment scheme used here is capable of restoring FEV_1 values to nearly pre-ABPA levels within 3 months. Even more important, the treatment allowed comparable long-term FEV_1 courses when comparing patients with their ABPA-naive, matched controls. This is in contrast to previous studies in which ABPA had been associated with an accelerated lung function decline.[19,20] In addition, two-thirds of our patients did not experience ABPA relapses.

The optimal clinical management of ABPA in CF is yet to be established. Systemic corticosteroids have long been used as the mainstay of treatment to suppress acute inflammatory responses.[13] The concomitant prescription of antifungals such as itraconazole has been suggested in recent guidelines.[21] However, its effectiveness has so far not been evaluated in a randomized controlled trial in patients with CF.[14] This paucity of evidence creates considerable variation between CF centers regarding drug combinations, dosing, and treatment duration for ABPA. In a recent UK survey, most consultants were found to use both corticosteroids and itraconazole to treat a first diagnosis of ABPA.

TABLE II. Assessment of prednisone side effects

Potential prednisone side effect	Patients	Controls	*P* value
P aeruginosa acquisition during follow-up	17 of 47 (36%)	18 of 71 (25%)	.22
P aeruginosa colonization at the end of follow-up	35 of 65 (54%)	74 of 127 (58%)	.65
CFRD diagnosis during follow-up	7 of 65 (11%)	12 of 127 (9%)	.77
Height percentile at baseline	20 (8-56)	26 (10-45)	.92
Height percentile at the end of follow-up	25 (4-57)	22.5 (7-45)	.94

Note. For comparison, baseline values pre-ABPA onset or at the end of the follow-up period are displayed where indicated. Data are shown as frequencies or median + IQR. Only patients younger than 18 y were considered when comparing height percentiles at the end of follow-up.

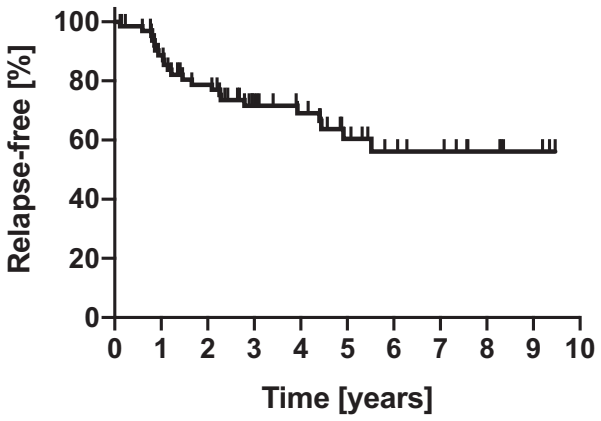

FIGURE 4. Time to first ABPA relapse. Symbols indicate when individual patient's follow-up ended without ABPA relapse.

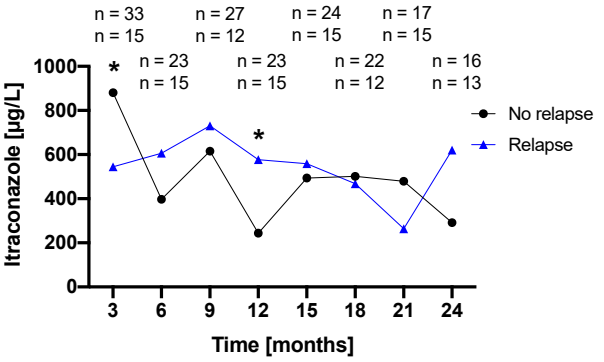

FIGURE 5. Itraconazole levels over time. Data are displayed as medians. Values on the *x*-axis reflect 3-mo intervals; eg, 6 summarizes levels obtained in months 4 to 6. Numbers indicate the number of patients without ABPA recurrence (black circles, top) and relapse patients (blue triangles, bottom) available for analysis. $*P < .05$.

However, one-third reported using only prednisolone.[22] In patients with asthma in the acute stage of ABPA, the use of either prednisolone or itraconazole as first-line treatment for 4 months was recently evaluated in a randomized manner. The authors reported a significantly higher treatment response rate in the glucocorticoid arm after 6 weeks.[23] However, itraconazole was effective in 88% of the subjects, and lung function changes as well as time to first relapse were comparable in both groups. In addition, adverse side effects were more common in glucocorticoid-treated subjects and the authors therefore argued for the combination of a much shorter glucocorticoid course with itraconazole.

The absence of glucocorticoid-related side effects in the patients treated for ABPA is the second major finding of this study. Steroid-induced hyperglycemia is especially of concern in patients with CF already at risk of developing CFRD. During follow-up, about 10% of both cases and controls were diagnosed with CFRD and we also could not observe any stunting of growth in pediatric patients with ABPA. ABPA treatment also did not significantly increase the risk to acquire *P aeruginosa* in the cohort under investigation. We were surprised to observe that *P aeruginosa* colonization was associated with a significantly lower risk to experience ABPA recurrence. This was somehow unexpected, and taking into account the predominance of T_H2 cells in the bronchoalveolar lavage fluid of *P aeruginosa*–infected patients with CF, one might have expected to find a rather increased allergic potential in these individuals.[24] However, Skov et al[25] found culture-positive ABPA to occur independently of the patients' *P aeruginosa* status. The first report on the capability of *P aeruginosa* to inhibit fungal growth was published in 1994,[26] and further studies demonstrated that *P aeruginosa* isolates and even *P aeruginosa* culture filtrates can inhibit *A fumigatus* biofilm formation.[27,28] Subsequently, Sass et al[29] identified pyoverdine, a siderophore promoting iron binding and uptake secreted by *P aeruginosa*, as the key molecule leading to *A fumigatus* growth inhibition. Pyoverdine restricts iron bioavailability for *A fumigatus*, and a positive correlation between pyoverdine production and antifungal activity was shown in *P aeruginosa* isolates from patients with CF.[29] Although our clinical observation awaits further clarification, it might be justified to monitor *P aeruginosa*–negative patients with ABPA even more closely for potential relapses.

We identified significantly lower itraconazole serum trough levels during the first 3 months of treatment in patients subsequently facing a relapsing disease course. It seems plausible that a more effective reduction of the antigenic stimulus early after diagnosis is beneficial with regard to later allergic exacerbations. The higher values in relapse patients between 9 and 12 months after the first treatment starts are probably resulting from 2 different trends. A group of patients had already relapsed by this time and prednisone reintroduction was associated with higher itraconazole target concentrations. On the other end of the spectrum, where patients had fully recovered and itraconazole treatment was due to be discontinued soon, dose adjustments might not have been executed vigorously anymore.

First, these findings underscore the potential benefit of TDM in guiding itraconazole treatment. Second, they illustrate how little is known about optimal trough concentrations in patients

TABLE III. Assessment of potential risk factor for ABPA relapse using a multiple logistic regression model

Potential risk factor for ABPA relapse	Adjusted odds ratio	Adjusted 95% CI	*P* value
A fumigatus culture−positive	0.63	0.06-6.28	.68
Candida albicans culture−positive	0.39	0.03-2.89	.38
A fumigatus−RAST-positive	10.36	1.15-175.0	.06
P aeruginosa culture−positive	0.04	0.003-0.37	**.01**
Itraconazole serum trough levels within first 3 mo of treatment	0.14	0.02-0.68	**.03**

Note. Bold text indicates statistical significance ($P < .05$).
RAST, Radioallergosorbent test.

with ABPA. Current recommendations on itraconazole concentration targets are mostly based on studies in neutropenic patients aiming to prevent breakthrough infections.[30,31] Collectively, trough concentrations of 500 to 1000 μg/L are recommended to prevent and treat invasive *A fumigatus* infections.[32] On the basis of observed median trough concentrations of 544 μg/L in patients facing relapses and 881 μg/L in relapse-free individuals, we would advocate for a target concentration of 1000 μg/L, at least in the first months of treatment. Our initial practice of treating patients with itraconazole for 12 months has been replaced during the course of the study by the intention to treat until total IgE levels have normalized. The incidence of ABPA in our cohort of some 400 pediatric and adult patients dropped in pediatric, adolescent, and adult patient groups during the observation period (see Figure E3 in this article's Online Repository at www.jaci-inpractice.org).

Several potential limitations of our study need to be acknowledged. Although this study is consistent with our previous work, the different diagnostic criteria for ABPA currently in use make studies difficult to compare. Having treated some patients for ABPA who did not fulfill the consensus conference minimal diagnostic criteria could have skewed results toward better long-term outcomes.[13] However, limiting our analysis to the patients matching the consensus conference diagnostic criteria revealed comparable long-term pulmonary function in patients with ABPA and in controls (see Figure E4 in this article's Online Repository at www.jaci-inpractice.org). In addition, our previous work has demonstrated that strict total IgE cutoff values promote underestimation of ABPA especially in young patients.[7] Because of the flexible TDM regimen, gaps between itraconazole measurements varied considerably, thereby limiting our ability to interpret AUC data. The retrospective nature of this study calls for further validation, which we plan to carry out in a prospective study design.

CONCLUSIONS

Taken together, our work presents a new approach combining short-term prednisone and long-term itraconazole to treat CF-related ABPA. The proposed treatment scheme was found capable of preserving lung function over years without detrimental glucocorticoid side effects.

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TABLE E1. Characteristics of treated ΔIgE episodes

Characteristic	Median (IQR)
Patients, n	65
Age (y) at first treatment	13.5 (3.7 to 42.0)
Follow-up period (y)	4.8 (2.3 to 6.5)
Treated episodes, n	106
ΔIgE (%)	205 (139 to 339)
Duration of rising total IgE levels before treatment (days)	172 (84 to 301)
ΔIgE/3 mo (%)	146 (73 to 339)
ΔIgE/3 mo $\geq$ 100%	60%
ΔFEV_1 (% predicted)	−25 (−37 to −15)
Previous failure of antibiotic treatment	51 of 106 (48%)
A fumigatus−RAST-positive	32 of 65 (49%)
A fumigatus−RAST-positive during follow-up period	20 of 33 (61%)
A fumigatus culture−positive*	5 of 98 (5%)
Reduction of total IgE levels after treatment	54% (27 to 72)

Note. Values are displayed as median + IQR or range in case of the age at first treatment.
RAST, Radioallergosorbent test.
**A fumigatus* was cultured from throat swabs in 68% of cases and sputum in the remaining 32%.

TABLE E2. Prednisone side effects in different age (pediatric patients <18 y) and sex groups

Event	Pediatric patients	Pediatric controls	*P* value	Adult patients	Adult controls	*P* value	Male patients	Male controls	*P* value	Female patients	Female controls	*P* value
P aeruginosa colonization at baseline	4 of 42	21 of 83	.06	14 of 23	35 of 44	.15	6 of 31	27 of 59	**.02**	12 of 34	29 of 68	.53
P aeruginosa acquisition during follow-up	11 of 38	9 of 62	.12	4 of 9	1 of 9	.29	8 of 25	4 of 32	.10	7 of 22	6 of 39	.19
CFRD diagnosis at baseline	1 of 42	1 of 83	>.99	4 of 22	3 of 44	.21	2 of 31	2 of 59	.61	3 of 33	2 of 68	.33
CFRD diagnosis during follow-up	3 of 41	2 of 82	.33	1 of 18	6 of 41	.42	2 of 29	2 of 57	.60	2 of 30	6 of 66	>.99

Note. Bold text indicates statistical significance ($P < .05$)

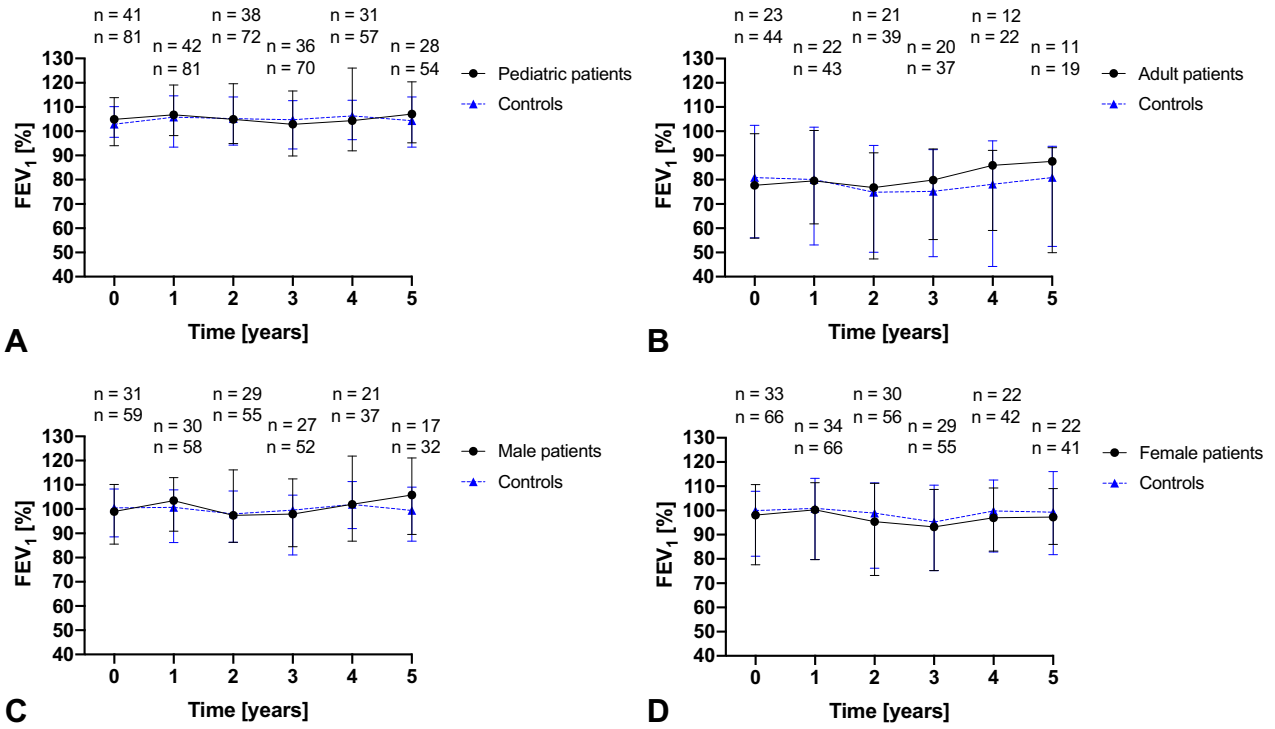

FIGURE E1. Long-term pulmonary outcome analyzed separately for age and sex. (**A**) Pediatric patients, (**B**) adult patients, **(C)** males, and **(D)** females alongside their matched controls.

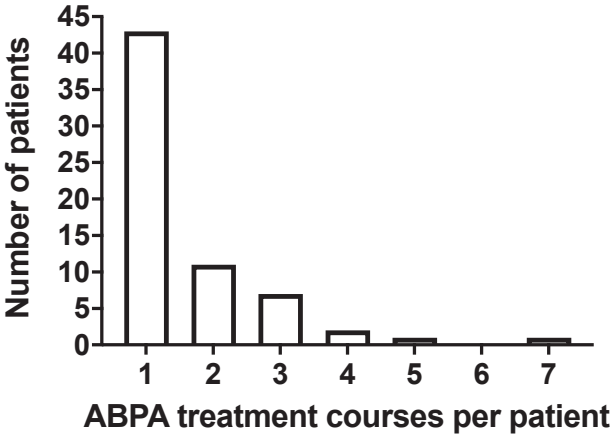

FIGURE E2. Number of ABPA treatment courses per patient. Of 65 patients, 22 experienced ABPA flares requiring treatment.

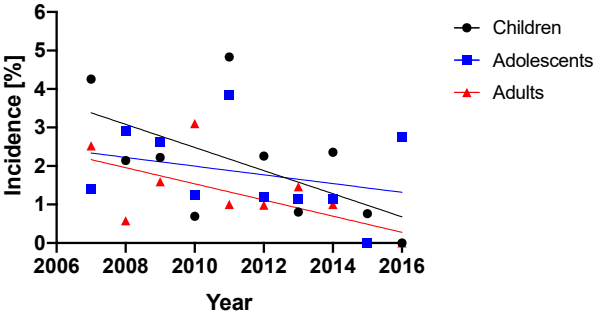

FIGURE E3. Incidence of ABPA in the Munich CF cohort in children (<12 y, black circles), adolescents (12 to <18 y, blue squares), and adults (≥18 y, red triangles). Lines indicate linear regression.

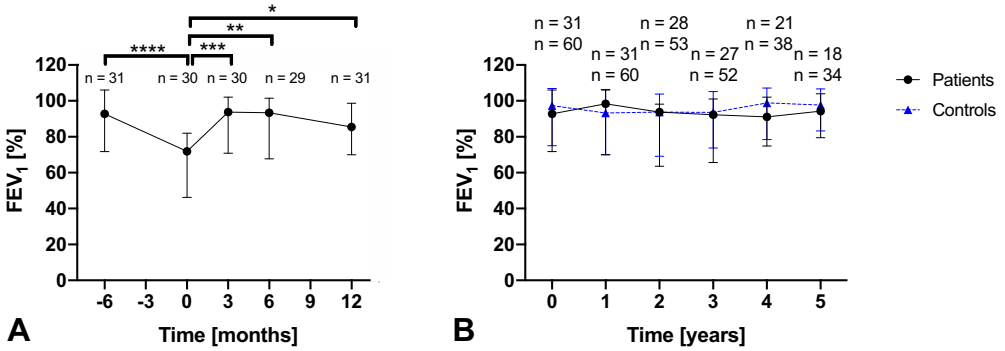

FIGURE E4. (**A**) Lung function recovery in the first year in patients diagnosed according to the consensus criteria. (**B**) Long-term follow-up on these patients. Symbols indicate median + IQR. Numbers represent the number of lung function measurements available for analysis at each time point. $*P < .05$, $**P < .01$, $***P < .001$, $****P < .0001$.