

Role of Inhaled Corticosteroids in the Management of Serological Allergic Bronchopulmonary Aspergillosis (ABPA)

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Abstract

Background and Aim The treatment of choice for allergic bronchopulmonary aspergillosis (ABPA) is oral corticosteroids (OCS). However, they are associated with numerous adverse effects. Inhaled corticosteroids (ICS) are associated with fewer side-effects; however, their role in the management of ABPA remains controversial. In this retrospective study, we evaluate the role of high doses of ICS in serological ABPA (ABPA-S).

Methods Patients with ABPA-S were treated with a combination of formoterol/budesonide (24-1600 micrograms per day), and followed up with history, physical examination, chest radiograph and total IgE levels at 6, 12, 18 and 24 weeks. Asthma control was evaluated using the Global Initiative for Asthma (GINA) criteria. OCS were initiated if the IgE levels continued to rise after six months of therapy with ICS.

Results There were 8 men and 13 women with a mean (SD) age of 39.3 (12.9) years. There was subjective improvement in all patients treated with ICS but none had complete control of asthma. After six months of therapy with ICS, the median IgE levels increased by 99.3%. After the initiation of OCS, there was complete resolution of asthma symptoms in 19 patients, and IgE levels fell by a median of 52.6% at six weeks. The median duration of follow-up was 15 months after OCS therapy. Eighteen patients achieved complete remission and three patients had a relapse in the first three months after stopping OCS. One patient required long-term OCS and was classified as glucocorticoid-dependent ABPA.

Conclusion High doses of ICS alone have no role in the management of ABPA-S and should not be used as first-line therapy. In patients receiving OCS or alternate therapy, ICS can be used as an add-on therapy for the control of symptoms of asthma.

Key words: ABPA, allergic bronchopulmonary aspergillosis, *Aspergillus fumigatus*, bronchiectasis, corticosteroids, glucocorticoids

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Introduction

Allergic bronchopulmonary aspergillosis (ABPA) is a pulmonary disorder that usually complicates the course of asthma and cystic fibrosis, and is caused by complex immunological reactions to *Aspergillus fumigatus*. (1) The prevalence of ABPA in asthma varies from 2-32%, whereas the

prevalence in cystic fibrosis ranges from 2-15% (1, 2). The condition was first described in 1952 by Hinson et al from the United Kingdom (3). It generally presents with poorly controlled asthma, hemoptysis, fever and weight loss. The Rosenberg-Patterson criteria are most often used for diagnosis (4, 5). However, there is no consensus on the number of criteria needed for diagnosis, and many patients do not fulfill all these criteria (1, 6, 7). High-resolution computed to-

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mography (HRCT) of the chest is the imaging modality of choice for the diagnosis of ABPA. Patients commonly present with central bronchiectasis (CB) on HRCT although there are patients of ABPA who otherwise fulfill all diagnostic criteria but lack demonstrable abnormalities on CT chest, and are labeled as serological ABPA (ABPA-S) (8). Patients with ABPA-S are generally believed to be the earliest stage of ABPA with a lesser degree of immunological activity (8).

Oral corticosteroids are currently regarded as the treatment of choice for ABPA associated with bronchial asthma (1, 7, 9). 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 (5, 10). Itraconazole, an oral triazole with a relatively low toxicity, is active against *Aspergillus* spp. in vitro and in vivo (11). The administration of itraconazole can eliminate *Aspergillus* in the airways and can theoretically reduce the allergic responses in ABPA (12-14). There are many patients who refuse treatment with oral glucocorticoids because of the fear of adverse reactions (15). Similarly, many patients cannot be treated with itraconazole because of financial constraints (10).

Inhaled corticosteroids (ICS) are associated with fewer side-effects compared to oral steroids, and have also been tried in ABPA. A double-blind multicenter placebo controlled trial in 32 patients suggested no superiority over placebo (16). However, this study used low doses of ICS (400 µg beclomethasone per day) and spacers were not employed. Small case studies have suggested variable benefits of ICS in the management of ABPA (17-20). Thus, the exact role of ICS in ABPA is poorly defined. We hypothesized that ICS alone has no role as first-line therapy in ABPA. To ascertain the role of ICS in ABPA, we chose glucocorticoid-naïve patients with ABPA-S, which is believed to be the milder form of the disease, and evaluated the role of high-dose ICS in its management.

Materials and Methods

The current study is a retrospective analysis of 21 patients of serologic ABPA diagnosed between July 2005 and June 2008 who refused treatment with oral corticosteroids and itraconazole for various reasons. We screened all patients with asthma presenting to our Chest clinic with an *Aspergillus* skin test. Patients who demonstrated type I responses in aspergillus skin test were further investigated for ABPA. Patients were diagnosed as ABPA-S if they met all the following criteria: (A) diagnosis of bronchial asthma (B) immediate cutaneous hyperreactivity to *A. fumigatus* antigen; (C) total IgE levels >1,000 IU/mL; (D) *A. fumigatus* specific IgE levels >0.35 kUA/L; and, (E) normal HRCT of the chest with or without the following criteria: (a) presence of serum precipitins against *A. fumigatus*; and, (b) absolute eosinophil count >1,000 cells/µL (10, 21-23). A written informed consent was taken from all patients and the study

was approved by the Institute Ethics Committee.

Aspergillus skin test

This test was performed using *A. fumigatus* antigen prepared in the Department of Medical Mycology. The skin test is performed by injecting 0.2 mL of the *Aspergillus* antigen (100 PNU/mL) intradermally in the forearm. For negative control, 0.2 mL of phosphate buffer saline is injected intradermally in the other forearm. The injection site was examined every 15 minutes for one hour, and then after six to eight hours. The reactions are classified as type I if wheal and erythema developed within one minute, reached a maximum after 10-20 minutes and were resolved within one to two hours; with the antigen arm skin reaction diameter being at least 8 mm more than the control arm. Type III reactions were defined by the presence of any amount of subcutaneous edema after six hours.

Upper Case Levels of serum IgE (total) and IgE (for *A. fumigatus*)

These levels were assayed with commercially available kits using the quantitative enzyme-linked immunosorbent assay (Demeditec diagnostics GmbH, Kiel, Germany) and the fluorescent enzyme immunoassay (UniCap Systems; Pharmacia Upjohn; Stockholm, Sweden).

High-resolution CT of the chest

CT was performed on a 16-row, multiple detector, CT scanner (LightSpeed Plus; GE Medical Systems; Slough, UK) with a 512 matrix size. The scans were obtained with a scan time of three seconds in the supine position at full end-inspiration from lung apex to base. The image acquisition was contiguous and the images (1.25 mm at 10-mm intervals) were reconstructed using the high-spatial-frequency algorithm.

Aspergillus fumigatus precipitins

These were detected by the Ouchterlony's gel diffusion techniques according to the method of Longbottom and Pepys (24).

Spirometry

Spirometry with bronchodilator reversibility was performed using commercial dry rolling seal spirometer (Spiro RS-232; P.K. Morgan Limited; Kent, UK). Patients were classified as mild, moderate and severe obstruction as per the standardized practice in our laboratory (25). Significant bronchodilator reversibility was considered if, after 200 micrograms of inhaled salbutamol, the forced expiratory volume in the first second (FEV₁) and/or forced vital capacity (FVC) increased by more than 12% and 200 mL (26).

Absolute eosinophil count

This count was performed by manually counting the cells on the peripheral blood film after determining the total white cell count on an automated blood cell analyzer.

Treatment protocol

The patients were treated with a combination of formoterol/budesonide at a dose of 24/1,600 µg per day using a transparent small volume valved spacer (Zerostat VT, Cipla, India). For any worsening of asthma symptoms, the patients were advised to take levosalbutamol 50 µg as needed. The patients were counseled that if the IgE levels show an increasing trend they would require treatment with oral glucocorticoids with an arbitrary limit set at 24 weeks. Oral glucocorticoids were introduced according to the following regimen: prednisolone 0.5 mg/kg for six weeks, 0.25 mg/kg for six weeks; then tapered by 5 mg every six weeks to continue for a total duration of at least six to twelve months. No patient received itraconazole or any other azole derivatives.

The baseline severity of asthma was assessed according to 2004 update of GINA, which also includes the effect of treatment including inhaled corticosteroids, on the disease severity (27). Patients were followed up with history, physical examination and chest radiograph at 6, 12, 18 and 24 weeks. At each visit, the asthma control was assessed using the GINA criteria as controlled, partially controlled and uncontrolled (28). We also evaluated the total IgE levels at each visit in these patients and observed the trend of the values during treatment with inhaled and oral corticosteroids. The percentage decline or elevation was calculated as: baseline IgE levels minus IgE levels divided by baseline IgE levels. Patients were classified as having *remission* if the IgE levels declined by more than 35 percent after three months of glucocorticoids, *relapse* if there were doubling of the baseline IgE levels irrespective of the patient's symptoms. Patients were finally categorized as *complete remission* if no ABPA exacerbations occurred over the next three months after stopping therapy or *glucocorticoid-dependent ABPA* if oral steroids were continually required for control of ABPA.

Statistical analysis

Data are presented as mean (SD), median (IQR) or number (percentage). Statistical significance was assumed at a p-value of less than 0.05.

Results

The study group included 21 (8 men and 13 women) patients of ABPA-S with a mean (SD) age of 39.3 (12.9) years. The median duration of asthma prior to diagnosis of ABPA was six years. All patients were being treated with ICS (400-800 micrograms equivalent of beclomethasone dipropionate) and long-acting β₂ agonists, but only three patients were using spacers. The baseline characteristics of these patients are shown in Table 1. Four patients had inappropriately received anti-tuberculous therapy for complaints of hemoptysis. The majority (52.4%) of the patients had moderate to severe obstruction on spirometry. The immu-

nological findings including absolute eosinophil counts, IgE levels (total), *A. fumigatus* specific IgE levels and *Aspergillus* precipitins are shown in Table 1.

There was subjective improvement in all patients after treatment with inhaled corticosteroids. However, none of the patients had complete control of asthma (Fig. 1). During treatment with inhaled corticosteroids, the IgE levels progressively increased (Fig. 2), and the median (IQR) IgE levels increased by 99.3 (52.6-122.4) percent compared to baseline. No chest radiographic abnormality was noted in any patient. After initiation of therapy with oral glucocorticoids, there was clinical improvement with the asthma symptoms fully controlled in 19 patients whereas only two patients had partially controlled asthma at six weeks follow-up. The median (IQR) IgE levels at six months were 5850 (3264.5-9393) IU per milliliter, and fell by a median (range) of 52.6 (11.8-81.4) percent at six weeks.

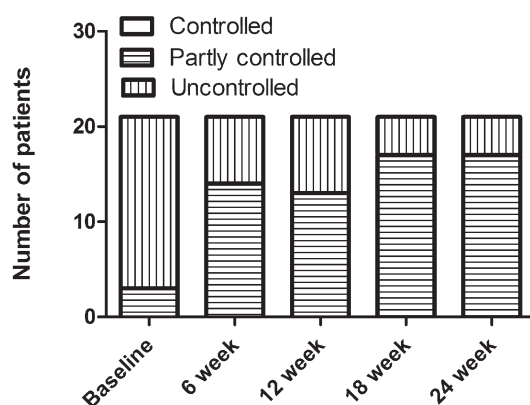
The median (IQR) duration of follow-up was 15 (13.3-19.5) months after the initiation of oral steroid therapy. All of the patients went into remission at three months. Eighteen (85.7%) patients had complete remission following cessation of oral steroids. The dosage of steroids was tapered, and therapy was stopped at a mean (SD) duration of 8.7 (1.4) months. Three (14.3%) patients had a relapse in the first three months after stopping oral steroids. All these patients were restarted on therapy with prednisolone. Of these three patients who relapsed, all achieved remission; however therapy could be stopped only in two patients (i.e. complete remission) at a mean (SD) duration of 11.5 (3.1) months. One patient was maintained on long-term treatment with steroid and was classified as having glucocorticoid-dependent ABPA.

Discussion

The results of this study suggest that inhaled corticosteroids (ICS) control the symptoms of asthma, but are ineffective in controlling the immunological activity in ABPA as the total IgE levels continued to increase despite control of asthma. The treatment of ABPA is primarily aimed at attenuation of the immunological activity, for which oral corticosteroids are the mainstay of therapy (1, 29), as is also evident from the current study. The other therapeutic target is attenuation of the fungal colonization of the tracheobronchial tree for which itraconazole has shown to be of some value (30). However, long-term systemic steroid therapy is prone to numerous adverse effects including diabetes mellitus, osteoporosis, infections and others (15). On the other hand, itraconazole is not only expensive but is also associated with several drug interactions and hepatic toxicity (31). The observation of the spectrum of effects of ICS in patients with asthma has led to the hypothesis that ABPA if diagnosed early in its course could be managed with ICS. Patients with ABPA-S represent the earliest stage of the disease with less severe immunologic findings compared to ABPA with central bronchiectasis (8). This was the rationale

Table 1. Baseline Characteristics Including Spirometry and Immunological Findings (n=21)

Demographic details	
Age (years), mean (SD)	39.3 (12.9)
Male gender	8 (38.1)
History	
Duration of asthma (years), median (IQR)	6 (3.5-10.5)
Hemoptysis, No. (%)	4 (19)
Expectoration of brownish black mucous plugs, No. (%)	2 (9.5)
Cigarette smoking, No. (%)	4 (19)
History of anti-tuberculous therapy	4 (19)
Spirometry, No. (%)	
Normal	6 (28.6)
Mild obstruction	4 (19.1)
Moderate obstruction	8 (38.1)
Severe obstruction	3 (14.3)
Bronchodilator reversibility	7 (33.3)
GINA severity of asthma, No. (%)	
Intermittent	0
Mild persistent	6 (28.5)
Moderate persistent	10 (47.6)
Severe persistent	5 (23.9)
Immunological findings	
Aspergillus skin test, No. (%)	
Type I	21 (100)
Type III	16 (76.2)
Absolute eosinophil count (cells/ μ L), median (IQR)	640 (250-1005)
<i>Aspergillus</i> precipitins, No. (%)	19 (90.5)
Total IgE levels (IU/mL), median (IQR)	2899 (1563-4772)
<i>A. fumigatus</i> specific IgE levels (kUA/L), median (IQR)	6.2 (1.6-11.7)

**Figure 1. Global Initiative for Asthma (GINA) control of asthma in patients during treatment with inhaled corticosteroids. There was improvement in asthma control however asthma could not be completely controlled in any patient.**

for including only patients with ABPA-S in this study.

ICS have minimal systemic side-effects but achieve high concentrations in the tracheobronchial tree and hence have been evaluated in the past in ABPA. The first study on the

use of ICS in ABPA was published in 1975 when Hilton and Chatterjee evaluated the use of beclomethasone 400 μ g daily in 15 patients of ABPA on oral steroids, and found adequate control of asthma in 13 patients (32). Oral steroids could be discontinued in eight patients while radiological worsening was witnessed in three patients (32). Following this, a multicentric double blind randomized controlled cross-over trial was conducted by the British Thoracic Association wherein 32 patients were treated with beclomethasone 100 μ g four times a day versus placebo (16). In this trial, 22 patients were already on maintenance therapy with oral steroids, and ICS treatment was associated with increase in prednisolone dose in eight patients in the treatment arm and 18 patients in the placebo arm. Despite treatment with oral and inhaled steroids, seven patients in the ICS arm had clinical exacerbations, and a higher number of radiological exacerbations were noted in this arm (16). Heinig et al. in a case report of two patients demonstrated clinical improvement in both patients with a combined treatment of oral and inhaled steroids (prednisolone 60 mg/day with decrease of 5 mg/week plus budesonide 800 μ g per day). ICS however did not control the immunological activity in one patient reflected by persistent elevations of IgE levels (17). Balter and Rebusk reported a good response to beclomethasone 500 μ g twice a day in a single patient of ABPA who refused oral steroids due to the fear of adverse effects of steroids which she had experienced in the past (18). In a report of two steroid dependent patients with ABPA, Imbeault and Cormier reported good response with beclomethasone 1,500 μ g every day, however patients received oral steroids for clinical and radiological exacerbations (19). Seaton et al in a study of five patients reported good spirometric and radiological response with ICS and short courses of self-administered oral steroids. The problem with this study was that the IgE levels were not measured (20).

Thus, there are numerous problems with the aforementioned studies. The studies have utilized varying doses of ICS, and many patients continued to receive oral steroids while also receiving ICS. Moreover, oral steroids were administered whenever there was clinical and/or radiological worsening. This makes it difficult to decipher whether the beneficial effects were solely due to ICS or otherwise. Moreover, in many studies, the clinical, radiological or spirometric criteria were used to define response to ICS in patients with ABPA, and IgE levels were not measured. The IgE levels are considered the most reliable index for monitoring the activity of the disease (33). It is important to remember that extensive infiltrates on chest radiograph may be witnessed even in an asymptomatic patient with ABPA, and symptoms are a poor guide to its activity of ABPA (34, 35). In fact, ABPA can complicate the course of apparently well controlled asthma and should be suspected in all asthmatics whatever the severity. In a large series of 155 cases of ABPA, 19% of ABPA had apparently well controlled asthma (21). The present study included only glucocorticoid naïve patients with ABPA-S who were solely

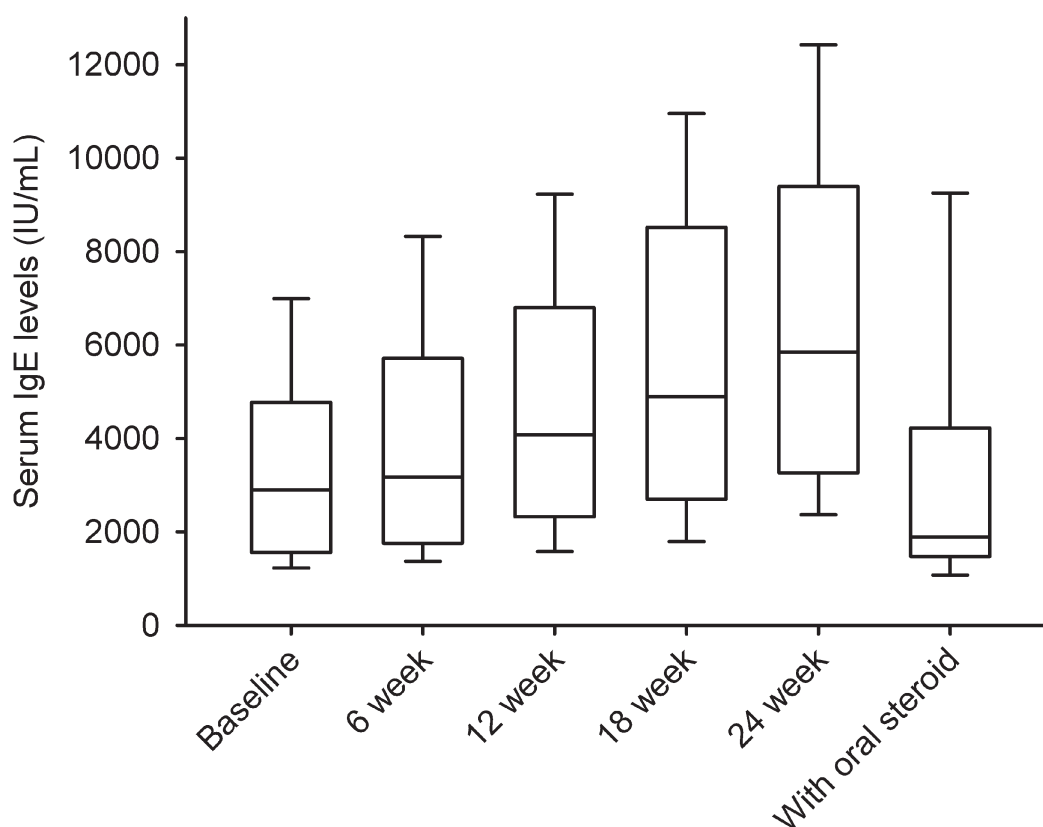


Figure 2. Box and whisker plots depicting serum IgE levels (total) in patients at baseline and during treatment with inhaled corticosteroids for six months. The median IgE levels increased during the treatment with inhaled corticosteroids. At six months all patients received oral steroids with a significant decline in IgE levels.

treated with ICS. Although the asthma was controlled to some extent with the use of ICS-LABA combination, the immunological activity could not be halted as reflected by increasing IgE levels.

The serum IgE levels decline after therapy with steroids (22, 36), and are also the most useful test for following up patients with ABPA. A doubling of the patient's baseline IgE levels indicates relapse of ABPA (37, 38). However, the explanation for the increased concentrations of IgE in ABPA is not known, and much of this IgE is not against antigens of *A. fumigatus* (39). A study evaluating IgE levels from peripheral blood lymphocytes (PBL) found IgE concentrations from PBL of ABPA patients not significantly different from controls. This could suggest that the PBL of ABPA do not form excess IgE, and IgE is probably released into the circulation from the site of primary involvement, i.e. the lung. However, the same study found that PBL during exacerbations of ABPA released significantly larger amounts of IgE than controls. This could mean that during exacerbations of ABPA, IgE-forming cells are released into the systemic circulation, most likely from the lung, since this is the only organ involvement in ABPA (40). Another study analyzing bronchoalveolar lavage fluid (BALF) in ABPA found higher concentrations of *A. fumigatus* specific IgE and IgA in BALF compared to serum suggesting local production of *Af*-IgE and *Af*-IgA in the BALF. However, the ratio of BALF

total IgE and *Af*-IgG levels were less than one suggesting that the lung is not the source of total serum IgE elevations but it reflects serum transudation. This may also be the reason that high-dose local steroid treatment had no demonstrable effects in the current and previous studies (41).

Finally, the present study is not without limitations. The first and most obvious limitation is the retrospective nature of the study. The other limitation is the small number of patients although this is the second largest study evaluating the role of ICS in ABPA. Finally, we did not measure the BALF IgE concentrations as they would have allowed us to interpret the exact reason for failure of ICS in this group of patients.

In conclusion, ICS alone have no role in the management of ABPA and should be used only for additional control of asthma in patients receiving oral steroids or alternate therapy.

The authors state that they have no Conflict of Interest (COI).

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