The effects of antifungal therapy on severe asthma with fungal sensitization and allergic bronchopulmonary aspergillosis

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ABSTRACT

Background and objective: Very little is known about the response rates to or appropriateness of treatment for patients with allergic fungal diseases of the lung. This study assessed the effect of antifungal therapy in patients with severe asthma with fungal sensitization (SAFS) and allergic bronchopulmonary aspergillosis (ABPA).

Methods: A retrospective cohort study of 33 adult patients who fulfilled the criteria for either SAFS (n = 22) or ABPA (n = 11) was conducted. All patients had received antifungal therapy for at least 6 months. The primary study end point was the effect of antifungal therapy on patients' lung function.

Results: Overall, total IgE values and radioallergosorbent test (RAST) for A. fumigatus markedly decreased after 6 months of therapy in both SAFS and ABPA patients (P = 0.004 and P = 0.005, respectively). Reduction was seen in the eosinophil count (P = 0.037), dose of oral steroids (P = 0.043) and courses of systemic steroids required (P = 0.041). Lung function also improved (P = 0.016). Four of 10 patients discontinued oral steroids after 6 months of therapy. Reduction in IgE levels (P = 0.015) and RAST for A. fumigatus was also observed (P = 0.006) for those patients treated for at least 1 year with antifungal drugs.

Conclusions: Both ABPA and SAFS patients benefited from oral antifungal therapy. The antifungal therapy may act by reducing the antigenic load, interacting with corticosteroids or by a direct immunological effect.

Key words: allergens, allergic bronchopulmonary aspergillosis, aspergillosis, asthma, itraconazole, voriconazole.

INTRODUCTION

Until recently oral corticosteroids were regarded as the only effective therapy for patients with allergic bronchopulmonary aspergillosis (ABPA). Since its introduction, oral itraconazole has shown therapeutic benefit in ABPA patients, in part by reducing the need for systemic steroids.1–6 The benefit of itraconazole has also been demonstrated in two double-blind, placebo-controlled trials in patients with ABPA.7,8 Individuals with steroid-dependent ABPA taking a 16-week course of itraconazole benefited from a reduction in oral steroid dose, lower total IgE levels, and improved exercise tolerance or resolution of pulmonary infiltrates.7 In another double-blind placebo-controlled trial involving stable patients with ABPA,8 itraconazole for 16 weeks was associated with improvement in immunologic parameters such as eosinophilia, total IgE, and Aspergillus-specific IgG suggestive of a potential anti-inflammatory and immunological effect.
There are well-accepted diagnostic criteria for ABPA. However, many patients with asthma have evidence of sensitization to many different fungi but do not fulfill these criteria. Recently, the term SAFS (severe asthma with fungal sensitization) was proposed for these patients. As the pathophysiological mechanisms underlying these conditions appear to be similar, a response to antifungal therapy might also be expected for patients with SAFS. The purpose of this retrospective study was to evaluate the effect of antifungal therapy in a cohort of patients with SAFS and ABPA.

METHODS

Study design

A retrospective cohort study was undertaken to assess the response to treatment of 33 adult patients with Aspergillus-related diseases treated with antifungal medication.

Study subjects

All consecutive patients attending a hospital chest clinic who fulfilled the clinical criteria for SAFS or ABPA and who had received at least 6 months of antifungal therapy were eligible for inclusion in the study.

Definitions

Diagnostic criteria for ABPA were: (i) asthma; (ii) immediate cutaneous reaction to *A. fumigatus*; (iii) total serum IgE ≥1000 IU/mL; (iv) elevated *A. fumigatus*-specific serum IgE levels (RAST); (v) precipitating antibodies to *A. fumigatus* in the serum; and (vi) central bronchiectasis. Minor diagnostic criteria were: (i) peripheral blood eosinophilia (often absent in patients receiving steroids); (ii) repeated detection of *Aspergillus* in sputum; (iii) a history of expectoration of brown plugs or flecks; and (iv) a history of recurrent pulmonary infiltrates (transient or fixed). Some patients with long-standing ABPA do not maintain detectable precipitins in their serum. Patients with ABPA were not specifically tested for immediate skin reactivity to *Aspergillus*; a raised serum specific IgE was regarded as equivalent.

Asthma severity was defined according to the British Thoracic Society (BTS) severity grade for asthma.

Criteria for the diagnosis of SAFS were: (i) severe (poorly controlled) asthma, BTS level four or five; (ii) total IgE <1000 IU/mL; and (iii) either a positive skin test or raised specific IgE to any fungus. In this study, we included only patients with SAFS related to *Aspergillus* species, with or without detectable serum precipitins to *A. fumigatus*.

The study protocol was approved by an independent local ethics committee and patient’s confidentiality was maintained at all times.

Study end points

The null hypothesis was that 6 months of treatment with antifungal drugs would have no impact on the lung function and laboratory parameters of patients with SAFS or ABPA. The primary study end point was the effect of antifungal therapy on patients’ lung function. Secondary end points were: number of hospitalizations or emergency room visits for respiratory diseases, total IgE value, RAST value for *A. fumigatus*, number of eosinophils in the peripheral blood, dosage of oral steroids, dosage of inhaled steroids and courses of systemic steroids.

Study methods

Clinical data from 6 months prior to the commencement of antifungal therapy (baseline) were obtained retrospectively, and were again collected after 6 and after 12 months of antifungal therapy. Patients who had received 6–12 months of antifungal therapy at the time of this study were evaluated for the 6-month end point only. The number of hospitalizations or emergency room visits and dose of steroids were routinely asked at clinic visits, and subject recall for these variables is thought to be quite reliable. Lung function was estimated by FEV₁ performed either in the laboratory or by the attending physician at the time of a clinic visit using a dry bellows wedge spirometer calibrated regularly. Prednisolone was used as the reference when comparisons of oral therapy with steroids were required. Similarly, beclometasone equivalent dose was used as reference for inhaled therapy with steroids.

Analysis

Descriptive statistics were used to summarize the data. Pearson’s chi-square test was used to evaluate categorical variables (Fisher’s exact test where appropriate). To compare continuous variables before and after antifungal therapy, non-parametric Wilcoxon signed ranks T test for related samples was used. For all comparisons, *P* values < 0.05 were considered statistically significant. All analyses were performed with the software SPSS 11.5.0 for Windows.

RESULTS

Patients’ characteristics

There were 33 patients included in the study, 22 of whom had a diagnosis of SAFS and 11 a diagnosis of ABPA (Table 1). All patients had asthma and were on treatment with inhaled steroids. The median duration of asthma was 42 years (range 5–68 years), which was similar for SAFS and ABPA patients. Most patients had severe asthma (BTS severity grade 4 in 71.9% and grade 5 in 25.0%). Women were significantly over-represented in the SAFS group (*P* = 0.003). As
Eosinophil syndrome was noted during the study. All patients received at least 6 months of therapy tentatively low itraconazole levels or clinical deterioration. Anti-fungal therapy was modified to voriconazole in three patients due to adverse effects, persistently low itraconazole levels or clinical deterioration. Itraconazole counts decreased by 33.5%, 36.9%, 26.7% for all patients (n = 22), ABPA patients (n = 11) and SAFS patients (n = 33). One additional patient with ABPA had a strongly positive IgE against Candida (55.6 IU/mL).

**Antifungal therapy**

All patients were initially treated with itraconazole, in dosages ranging from 100 to 450 mg daily (median 300 mg daily). Mean itraconazole levels were therapeutic (>5 mg/L) for 75% of patients. Side effects occurred in 19.3% of patients, and included tendinitis (6.4%), oedema (3.2%), diarrhoea and rash (3.2%), abnormal liver function (3.2%) and abdominal pain (3.2%). Antifungal therapy was modified to voriconazole in three patients due to adverse effects, persistently low itraconazole levels or clinical deterioration. All patients received at least 6 months of therapy (range 6–60 months). No patient with overt Cushing’s syndrome was noted during the study.

**Evaluation after 6 months of antifungal therapy**

Patients’ response to 6 months of antifungal treatment is summarized in Figure 1. Total IgE values decreased significantly by 24.5% in SAFS patients (P = 0.004) and 36.8% in ABPA patients (P = 0.005). RAST for A. fumigatus decreased significantly by 14.8% in the overall population studied (P = 0.005), and by 34.1% in SAFS patients (P = 0.019). Although RAST values actually increased by 21.6% in ABPA patients (P = 0.139), a decrease of 30.5% (P = 0.017) was seen when the only ABPA patient for whom RAST values were higher in ABPA patients (n = 2) and 27.3% of SAFS patients (n = 6). One additional patient with ABPA had a strongly positive IgE against Candida (55.6 IU/mL).

Table 1  Baseline characteristics of patients included in the study

<table>
<thead>
<tr>
<th></th>
<th>SAFS (n = 22)</th>
<th>ABPA (n = 11)</th>
<th>P value</th>
<th>All patients (n = 33)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women (%)</td>
<td>16 (72.7%) (16/22)</td>
<td>2 (18.2%) (2/11)</td>
<td>0.003</td>
<td>18 (54.5%) (18/33)</td>
</tr>
<tr>
<td>Age, years (range)</td>
<td>51.5 (34–75) (22/22)</td>
<td>52.0 (42–67) (11/11)</td>
<td>0.925</td>
<td>52.0 (34–75) (33/33)</td>
</tr>
<tr>
<td>Total IgE, IU/mL (range)</td>
<td>337 (76–990) (22/22)</td>
<td>3 317 (1 000–39 000) (11/11)</td>
<td>&lt;0.0001</td>
<td>600.0 (76–39 000) (33/33)</td>
</tr>
<tr>
<td>RAST for A. fumigatus, IU/mL (range)</td>
<td>3.6 (0.5–34.9) (21/22)</td>
<td>51.2 (0.8–350.0) (11/11)</td>
<td>0.001</td>
<td>8.75 (0.5–350.0) (33/33)</td>
</tr>
<tr>
<td>% with positive precipitins to A. fumigatus</td>
<td>28.6% (4/14)</td>
<td>71.4% (5/7)</td>
<td>0.159</td>
<td>27.3% (9/21)</td>
</tr>
<tr>
<td>Duration of asthma, years (range)</td>
<td>35.0 (7–68) (21/22)</td>
<td>44.0 (5–64) (11/11)</td>
<td>0.180</td>
<td>42.0 (5–68) (32/33)</td>
</tr>
<tr>
<td>FEV₁, L, (range)</td>
<td>1.60 (1.30–3.00) (17/22)</td>
<td>1.75 (1.40–3.60) (10/11)</td>
<td>0.223</td>
<td>1.69 (1.30–3.60) (27/33)</td>
</tr>
<tr>
<td>Inhaled steroid dose, µg daily (range)</td>
<td>1000 (400–2000) (22/22)</td>
<td>1 000 (800–2 000) (11/11)</td>
<td>0.985</td>
<td>1 000 (400–2 000) (33/33)</td>
</tr>
<tr>
<td>Eosinophils ×10⁹/L, (range)</td>
<td>0.395 (0.10–1.81) (20/22)</td>
<td>0.330 (0.06–0.76) (9/11)</td>
<td>0.908</td>
<td>0.37 (0.01–1.81) (29/33)</td>
</tr>
<tr>
<td>% continuously on oral steroids</td>
<td>22.7% (5/22)</td>
<td>45.5% (5/11)</td>
<td>0.240</td>
<td>31.3% (10/33)</td>
</tr>
<tr>
<td>% exacerbations requiring steroids†</td>
<td>50.0% (11/22)</td>
<td>36.4% (4/11)</td>
<td>0.458</td>
<td>45.5% (15/33)</td>
</tr>
<tr>
<td>% hospitalized for asthma†</td>
<td>13.6% (3/22)</td>
<td>18.2% (2/11)</td>
<td>1.000</td>
<td>15.2% (5/33)</td>
</tr>
</tbody>
</table>

† In 6 months before starting antifungal therapy.

Continuous variables are presented as median values and range. Fractions represent the number of patients tested for the particular variable.

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receive any additional steroids in the first 6 months of antifungal therapy. The dosage of inhaled steroids was not modified after antifungal therapy ($P = 0.577$ for all patients). Similarly, there was no significant reduction in the number of hospitalizations or emergency room visits due to respiratory diseases during the antifungal treatment ($P = 0.589$ for all patients); however, only five patients had been admitted to the hospital in the 6 months preceding the start of antifungal therapy.

**Evaluation after 12 months of antifungal therapy**

From the 33 patients initially included in the study, data from 17 patients who were on treatment with antifungal drugs for more than 1 year were obtained (13 SAFS patients and 4 ABPA patients). In these patients overall, total IgE values decreased by 22.6% ($P = 0.015$); however, there was no significant reduction in the respective subgroups (SAFS, reduction by 10.2%; $P = 0.155$; ABPA, reduction by 41.1%; $P = 0.068$). For the group overall, RAST values significantly decreased (average reduction 32.7%; $P = 0.006$); however, there was no significant reduction in the respective subgroups (SAFS, 27.4% reduction, $P = 0.053$; ABPA, 40.9% reduction, $P = 0.068$). A non-significant decrease was observed in the dosage of inhaled steroids (in all patients an 8.6% reduction, $P = 0.059$; in SAFS patients a 6.3% reduction, $P = 0.180$; in ABPA patients a 13.3% reduction, $P = 0.157$). Overall, antifungal therapy at 12 months resulted in no statistically significant changes in the key variables of the number of eosinophils (2.7% reduction, $P = 0.779$), dosage of oral steroids (59.0% reduction, $P = 0.109$), courses of systemic steroids (54.1% reduction, $P = 0.589$), FEV$_1$ values (reduction by 290 mL, $P = 0.726$) and the number of hospitalizations (11.1% reduction; $P = 0.257$), compared with baseline.
DISCUSSION

Asthma is common, affecting at least one in every seven children and one in 25 adults in the United Kingdom. Although most asthma patients have mild symptoms, a minority of patients suffer from severe symptoms requiring multiple hospital admissions. Severe asthma seems to be strongly associated with atopy, especially to mould allergens. In addition, a strong temporal relationship exists between high environmental spore counts and asthmatic attacks.

Asthma deaths and admissions to hospital in the United Kingdom of patients under the age of 35 years have been shown to coincide with the summer-autumn increase in ambient mould spores. Among patients with persistent asthma requiring specialist referral, 20–25% will have skin test reactivity to Aspergillus or other fungi. A. fumigatus plays an important role as an allergen in these patients.10 toll-like receptor profiles have now been detected.15 The limited number of patients reduced the power of the study, which was evident when the subgroups of patients with SAFS or ABPA were evaluated separately. After 6 months of antifungal therapy, patients with SAFS showed lower IgE levels, A. fumigatus-specific IgE levels and eosinophils. No significant improvement occurred for lung function (P = 0.075) and need of systemic steroids (P = 0.062). Analyses of results after 1 year of therapy for SAFS patients were limited by the small number of patients. Results for patients with ABPA were similar, except that eosinophil counts and courses of systemic steroids did not improve after 6 months of antifungal therapy.

The results of this retrospective study support the findings from the FAST study, a double-blind placebo-controlled randomized trial of itraconazole in patients with SAFS. In this multicentre study, SAFS patients treated with itraconazole for 32 weeks had a significant improvement in quality of life, which was evaluated by the Asthma Quality of Life Questionnaire (AQLQ) score. In addition, the benefit of antifungal treatment was demonstrated by total IgE levels, respiratory function and rhinitis score. Follow-up 4 months after discontinuation of the assigned therapy showed the AQLQ score had reverted to nearly pre-study levels. Similar findings were observed for the rhinitis score, suggesting that continuing antifungal therapy beyond 8 months is important for maintaining quality of life in these patients. Based on the results from the current cohort and the FAST study, a minimum of 6–8 months of antifungal therapy seems to be required by these patients, although larger studies would be required to evaluate more accurately the ideal duration of antifungal therapy. As with the FAST study, results from this cohort showed that therapy with itraconazole was associated with considerable toxicity. However, few
patients needed the antifungal therapy to be modified due to side effects, and the clinical benefit of antifungal therapy seemed to outweigh any associated risk. In order to minimize the risk of antifungal resistance and toxicity, therapy is best guided by the monitoring of itraconazole serum levels.

Three possible mechanisms of action are postulated to explain the benefits of antifungal therapy for allergic fungal disease. Reduction of the local fungal airway load (e.g. colonization of the lung) may reduce the overall allergic response. Systemic antifungal therapy may also reduce fungal exposure in the sinuses, gut and/or skin. Understanding whether the impact is local to the lung or systemic is important when considering local inhaled antifungal therapy versus systemic therapy.

Alternatively, itraconazole may increase inhaled steroid exposure resulting in a more anti-inflammatory effect, although we have no direct evidence for this. Itraconazole (the antifungal drug most frequently used in this study) is known to be an inhibitor of CYP3A4. Patients treated with itraconazole show higher exposure to budesonide and probably fluticasone; beclometasone has not been tested. Itraconazole has no effect on prednisolone levels (although voriconazole increases prednisolone exposure by approximately 30%). There are also reports of drug interactions using inhaled budesonide and fluticasone in combination with itraconazole resulting in adrenal suppression in patients with ABPA.

Immunomodulatory effects could contribute to the response to itraconazole. Itraconazole has been shown to suppress in a dose-dependent manner the secretion of type 2 cytokines (IL-4 and IL-5) in both T cells obtained from patients with atopic dermatitis and healthy controls (58% inhibition by 1 mmol/L of itraconazole). In addition, itraconazole has been shown to suppress the elicitation phase of the allergic contact hypersensitivity reaction in mice challenged with hapten, perhaps via inhibition of interferon-γ production from hapten-immunized effector T cells. There is no effect of itraconazole on polymorphonuclear leucocyte oxidative metabolism and phagocytosis, whereas suppression of neutrophil random motions, chemotaxis and metabolism (at 10 μg/mL) are demonstrable. Itraconazole also inhibits the generation of allospecific cytolytic activity in human mixed lymphocyte culture (an effect as suppressive as cyclosporine A). In one investigation, a large number of genes encoding chemokines and inflammation-related cytokines were strongly up-regulated in the presence of voriconazole. Hohl et al. also showed increased TNF-α production by mouse alveolar macrophages after incubation with A. fumigatus in the presence of 0.5 μg/mL voriconazole. These three possible mechanisms are not mutually exclusive.

In summary, results from this retrospective study suggest that both ABPA and SAFS patients benefit from a 6-month course of antifungal therapy, which is in accordance with clinical experience and evidence from a randomized clinical trial. The primary mechanism of azole action in this context as well as the benefit of longer therapy with antifungal drugs requires considerably more research.

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