Therapy of Allergic Bronchopulmonary Aspergillosis

Jordan N. Fink

Allergy-Immunology Division, Medical College of Wisconsin, Milwaukee, Wisconsin, USA

ABSTRACT

The management of ABPA depends on the extent and stage of the disease. Underlying asthma should be controlled with environmental changes, pharmacologic and immunotherapy. Baseline examinations and evaluations of pulmonary function, airway and parenchymal anatomy, and serum total IgE levels are important and should be re-evaluated based on the clinical course of the patient. The mainstay of pharmacotherapy for ABPA remains oral corticosteroids. The dose and duration of treatment in the initial stage of the disease depends on when it was diagnosed as well as the patient’s clinical course. Anti-fungal agents should be considered as adjunctive. Clinical data suggests that the early institution of treatment is likely to prevent progression of ABPA to end-stage fibrosis.

Key words: Allergic bronchopulmonary aspergillosis, Therapy, Corticosteroids, Serum IgE.

[Indian J Chest Dis Allied Sci 2000; 42 : 221-224]

INTRODUCTION

The diagnosis and treatment of allergic bronchopulmonary aspergillosis (ABPA) includes evaluation of the patients asthma and constitutional features, skin test reactivity to Aspergillus extract, evaluation of serologic studies for total and Aspergillus specific IgE and eosinophil levels, evaluation of pulmonary function for level of impairment, review of chest x-rays for resolution of or an increase in infiltrates, CT scan for bronchiectasis, and control of underlying respiratory disorders such as asthma, sinusitis, and rhinitis. While prednisone remains the mainstay of therapy for control and stability of ABPA, appropriate therapy of underlying asthma with anti-inflammatory and bronchodilator agents is essential. Immunotherapy is also useful when indicated for control of the inflammatory response. Similarly, therapy for underlying allergic rhinitis and/or sinusitis should be vigorous to reduce their influence on the asthmatic response.

Baseline studies of patients with ABPA should include a chest x-ray and thin section chest computerized tomography to evaluate the patients for and the degree of bronchiectasis, complete pulmonary functions, and total and Aspergillus specific serum IgE levels. If there is suspicion that there may be Aspergillus fumigatus in the patient’s environment, it should be identified by inspection and culture and eliminated as avoidance is important in therapy. Areas such as crawl spaces, moist basements, areas under carpeting laid over concrete, backyard or neighbourhood compost piles, and construction sites may all be focuses of growth of the organism.

Correspondence: Prof. Jordan N. Fink, V.A. Medical Center, Research Service 151-I, 5000 West National Avenue, Milwaukee, WI 53295, USA; Tele.: (414) 384-2000 Extn. 1510; Telefax: (414) 382-5374.
PHARMACOTHERAPY

Prednisone remains the mainstay of therapy for ABPA. During the acute episode manifested by increased asthma, pulmonary infiltrates and constitutional symptoms, prednisone should be administered at a dose of 0.5 mg/kg for two weeks then reduced to an alternate day regime for up to three months. Repeat chest x-ray in one month should demonstrate clearing of the infiltrates. If additional infiltrates occur or resolution of the original infiltrates is delayed, the dose of prednisone should be increased to 60 or more mg per day for two more weeks with subsequent conversion to alternate day therapy. The total serum IgE level regresses along with the infiltrates. The failure of the total serum IgE level to decrease suggests continuation of active disease and requires additional corticosteroids.

Following successful infiltrate clearing there is a reduction in total serum IgE and remission of the patient’s symptoms. The total serum IgE level should then be followed at regular intervals. In patients with ABPA, the total serum IgE remains stable at an elevated level rather than returning to normal levels even with high dose prednisone therapy; such stability is usual in remission. Adding additional prednisone does not usually reduce the level further. Patients under control may have levels of 3000 μg IgE/ml serum when asymptomatic which increases to 15000 μg IgE/ml serum with active disease. Serial total serum IgE levels are therefore important in follow-up care. A sudden doubling of total serum IgE levels over baseline usually heralds activity of disease. Such activity can be aborted or even prevented with increased prednisone at the time the elevated IgE is noted.

Prednisone therapy should be administered to ABPA patients with recurrent exacerbations or for control of severe persistent asthma. Serial serologic and radiologic evaluations are also important in such patients. Serial pulmonary function evaluation is valuable in monitoring patients with ABPA. The pulmonary infiltrates of ABPA reduce diffusion capacity, vital capacity, one-second forced expiratory volume and total lung capacity and are usually normalized by prednisone therapy. However, the patient’s lung air flow and volume may also be influenced by the activity or quiescence of the underlying asthma. Most important, with recurrent episodes of pulmonary inflammation of ABPA, irreversible obstruction and extensive bronchiectasis may occur and may lead to fibrosis. It is thus of value to repeat pulmonary CT evaluation every few years to determine stability or progression of disease, which also may influence the extent of corticosteroid therapy. Determination of pre and/or post exercise arterial blood gas oxygen levels may also help the evaluation of disease stability. Evidence suggests that if ABPA can be stabilized the progression of disease to its fibrotic end stage can be prevented.

The action of prednisone in ABPA is not directly on Aspergillus as the organism grows well in prednisone containing media. The effect of prednisone is anti-inflammatory reducing conditions favouring the growth of Aspergillus. Peripheral, pulmonary, and sputum eosinophilia are reduced and the organism disappears from the sputum. Reduction in pro-inflammatory cytokines and mucus secretion and stabilization of underlying asthma are important in reducing the ABPA flare. Prednisone can also inhibit the inflammatory process of bronchiectasis, but it does not alter the already induced structural damage.

Patients who have remission of ABPA may discontinue prednisone. The remission may last for years or may be permanent. In patients with recurrent flares of ABPA or in those with severe persistent asthma, long-term corticosteroid therapy may be necessary to control their asthma. Serial total serum IgE levels and chest x-rays should be evaluated in such patients, especially if their asthma becomes difficult to control or persists. Reactivation of ABPA in spite of steroid therapy needs to be considered in such patients. However, the characteristic pulmonary infiltrates may not be evident on examination and treatment may need to be empirical. In ABPA, severe persistent steroid dependent asthma is the common clinical presentation. The
additional airway inflammation and airway remodelling induced by the immune response to *Aspergillus* may be the cause of this persistence.

There are no controlled studies evaluating the effectiveness of long-term oral corticosteroids in ABPA. However, the literature suggests that maintenance with prednisone over the long-term may prevent the end-stage fibrotic pulmonary disease. In a long-term follow up of 28 patients with ABPA on prednisone for 11 years, there was no deterioration in forced expiratory volume in one second or forced vital capacity. However, in another study of 17 patients with end-stage fibrotic disease treated with long-term corticosteroids, four of 11 survivors had severe respiratory impairment. In this study, the prognosis was poor in patients with an initial forced expiratory volume in one second of less than 800 ml after two weeks of prednisone administered at 0.5 mg/kg or higher daily dose. In another study of 84 patients followed for a mean of 3.7 years, one-third of 24 patients with end-stage fibrotic lung disease, all of whom had fibrosis at the time of diagnosis, died. The prognosis of patients with initial one second forced expiratory volumes of between 800 ml and 2.1 litres was not as poor with the administration of up to 40 mg of corticosteroid daily. In the remaining patients, none progressed to fibrosis but required continuous corticosteroids for asthma control.

In patients in the fibrotic stage of ABPA, sputum volume may increase and organisms such as *Pseudomonas*, atypical mycobacteria, and *Staphylococcus* may be present. This is similar to that seen in cystic fibrosis. Measures such as postural drainage and antibiotics may be useful, but with deterioration, exercise tolerance decreases and oxygen therapy may be needed. DNA-ase preparations may be used to liquefy the sputum and provide some relief of symptoms. Lung transplantation may be an alternative for such patients.

**OTHER TREATMENTS**

Other treatments for ABPA have been described and may be of value. High doses of inhaled beclomethasone may be useful in some patients and may allow reduction in the dose of oral corticosteroids. However, there have been no controlled studies with beclomethasone, triamcinolone or fluticasone in ABPA. Antifungal agents have been used to eradicate *Aspergillus* from the bronchial tree, hopefully reducing the need for corticosteroids, and thus stabilizing the patient. The administration of Amphotericin B by aerosol, along with corticosteroids, has been shown to be useful in small numbers of cases. After a one-year study with ketoconazole in patients with ABPA, asthma was improved and *Aspergillus* specific serum IgG levels were significantly reduced. The newer imidazoles such as itraconazole and fluconazole have less side effects than ketoconazole. These drugs may be effective in eliminating *Aspergillus* from the sputum and may foster reduction in the dose of corticosteroids needed for control. Long-term safety and the effect of these drugs on progression of ABPA have not yet been studied. Other anti-fungal agents such as nystatin and pimaricin have been tried in ABPA, but in a limited number of patients. Thus, corticosteroids remain the mainstay of treatment for this disease.

In patients with atopic asthma, environmental controls and allergen immunotherapy should be provided. Removal of sources of *Aspergillus* such as nearby compost piles or eliminating basement moisture may be helpful in reducing exposure to the organism. Immunotherapy with environmental allergens may be helpful in reducing asthmatic episodes. The use of *Aspergillus* as immunotherapy in ABPA has not been studied. It may induce adverse reactions or may play a role in inducing a vasculitis as a result of immune complexes developing from antigen-IgG antibody and complement interaction, while this is possible, the large antibody excess would reduce the inflammatory nature of the formed complexes.

**ACKNOWLEDGEMENTS**

This work was supported by the Veterans Administration Research Service.
REFERENCES


