

Editorials

Antifungal therapy for allergic
bronchopulmonary aspergillosis

Key words: Asthma, *Aspergillus*

Sensitization to molds is relevant in asthma because it is associated with a generally more severe condition.¹ Approximately one third to one fourth of adult subjects with asthma might have sensitization to *Aspergillus* mold,² though a minority of these subjects develop allergic bronchopulmonary aspergillosis (ABPA). ABPA, first well characterized as a distinct entity by Hinson et al³ in 1952, is a type of pulmonary eosinophilic reaction that can be defined as the occurrence of a pulmonary infiltrate in a subject with asthma, peripheral blood eosinophilia, and evidence of immunologic sensitization to *Aspergillus*.^{4,5} The mechanism of the disease implies both an IgE- and an IgG-mediated^{6,7} process of variable balance and intensity, along with the activity of the disease process^{8,9} and a combination of type I and type III¹⁰ immune responses. The lung infiltrates, generally of the frank pneumonic type with atelectasis or the glove-finger type, cause the development of bronchiectasis¹¹—more likely so if the infiltrates do not clear rapidly. Subjects with ABPA have more lung function impairment than subjects paired for the severity of asthma but no ABPA.¹²

Management of ABPA is relatively easy in subjects who have rare flare-ups, but it is difficult in those who experience frequent recurrences of pulmonary infiltrates. The production of “plugs” in the sputum containing eosinophils and hyphae of *Aspergillus* is generally regarded as a convincing clinical marker of flare-ups, but many subjects can have asymptomatic episodes, which makes early identification of flare-ups difficult. Total IgE can increase before evidence of infiltrates appears on chest radiographs. It has been well known for years that oral steroids have a most beneficial effect on the clearing of acute infiltrates. Whereas the use of oral steroids on occasion is less of a concern, frequent or continuous use might lead to significant side effects. There are subjects in whom oral steroids must be administered continuously to prevent recurrence of infiltrates, though a significant proportion of them are on an alternate-days regimen.

Abbreviation used

ABPA: Allergic bronchopulmonary aspergillosis

The efficacy of antifungal therapy for ABPA has been assessed more recently, first in uncontrolled studies¹³ and subsequently in a randomized trial.¹⁴ The latter showed that itraconazole, an orally administered triazole at a dose of 400 mg daily, efficiently prevents the recurrence of radiographic shadows¹⁴ without evidence of toxicity. In addition, with itraconazole, one half of the subjects with ABPA were able to reduce their intake of oral steroids.¹⁴ An open study further showed that this approach not only reduced the frequency of flare-ups but also reduced blood eosinophils and total IgE levels and significantly improved FEV₁.¹⁵

In this issue of the Journal, Wark and coworkers,¹⁶ in a randomized, double-blind, placebo-controlled trial, explore the efficacy of itraconazole given 400 mg daily on airway inflammation assessed by (1) sputum eosinophils and eosinophil cationic protein, (2) serologic markers of severity assessed by total serum IgE and specific IgG to *Aspergillus*, and (3) requirement in oral steroids for respiratory symptoms. All of these parameters significantly improved in the active group. However, it is relevant to point out that the improvement was not defined by the authors in terms of reduction of radiographic infiltrates, inasmuch as their study population consisted of subjects with stable ABPA who were followed for a relatively short period of 16 weeks.

As discussed by the authors, treatment with itraconazole targets the reduction of *Aspergillus* load in the airways, which in turn decreases immune activation. However, itraconazole might also enhance the effect of methylprednisolone,¹⁷ though the same has not been found in the case of prednisolone.¹⁸ If this is the case, it would be interesting to test the effect of itraconazole in asthmatic subjects with sensitization to *Aspergillus* but no evidence of ABPA, and even in asthmatic subjects requiring oral steroids, to determine whether the dose of steroids can be reduced by the addition of itraconazole.

Whatever the mechanism of action of itraconazole and the possibility of other therapeutic indications in asthma, it is clear from the results of the studies by Wark and colleagues¹⁶ and others^{14,15} that itraconazole represents what can be considered an interesting breakthrough in the management of ABPA, both to prevent recurrences of infiltrates and to improve airway inflammation, serologic evidence of disease activity, and the general clinical

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situation. This is good news for patients with a rather rare but most disabling disease.

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