

Asthma treatment and asthma prevention: A tale of 2 parallel pathways

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Three recent clinical trials used different study designs to test the hypothesis that early introduction of inhaled corticosteroids in infants and young children at high risk for the development of asthma could change the natural course of the disease. All 3 trials reached the same conclusion: treatment requirement, symptom frequency while off treatment, and lung function did not differ between children receiving active drug or placebo, with outcomes measured 2 to 4 years after randomization. These findings challenge the concept that the inflammatory processes that cause asthma symptoms and are responsive to inhaled corticosteroids are also responsible for the chronic changes in airway structure and function that are believed to predispose to the development of persistent asthma. This conclusion is supported by studies showing that bronchial hyperresponsiveness, independent of current asthma symptoms, is associated with subsequent deficits in airway function growth during childhood. Successful strategies for the prevention of asthma will require a better understanding of the genetic, environmental, and developmental factors that predispose toward inappropriate responses to airway injury. Abnormal airway remodeling and persistent dysregulation of airway tone might be the final common pathway for different disease mechanisms, and this might explain the heterogeneity of clinical phenotypic syndromes that go under the common label of "asthma." (*J Allergy Clin Immunol* ■■■■;■■■;■■■-■■■.)

Key words: Asthma, bronchial, hyperresponsiveness, inhaled corticosteroids, lung function, remodeling

One of the most important issues addressed by the National Heart, Lung, and Blood Institute (NHLBI) Asthma Networks has been the potential for daily treatment with inhaled corticosteroids (ICSs) to change the natural course of the disease. This hypothesis was deeply rooted in what has been the dominant theory about asthma

Abbreviations used

BHR: Bronchial hyperresponsiveness
CAMP: Childhood Asthma Management Program
ICS: Inhaled corticosteroid
NHLBI: National Heart, Lung, and Blood Institute
PEAK: Prevention of Early Asthma in Kids

in the last 20 years, namely that asthma is an inflammatory disease. Since the early 1990s, several studies of bronchoalveolar lavage samples clearly have shown that in persons with persistent asthma, increased concentrations of inflammatory cells and mediators were present in the lungs, even in asymptomatic subjects.¹ This discovery and the finding that the intensity of the local inflammation (often characterized by the presence of eosinophils and other T_H2-type cells and mediators) correlated with bronchial hyperresponsiveness (BHR) and with symptom severity² produced a major paradigm shift. Asthma was no longer considered a disease of acute flares separated by normalcy but rather a chronic condition in which persistent expression of airway inflammation predisposes to and is the underlying cause of its main manifestation, reversible bronchial obstruction. It flowed naturally from this conception that instead of treating asthma only when symptoms occur, suppressing persistent inflammation had to be the strategy of choice. National and international guidelines fostered the use of daily chronic therapy with ICSs as the mainstay for the treatment of the disease.

There is little doubt that this strategy has had a major positive effect on the improvement of asthmatic patients' quality of life and on decreasing morbidity and mortality related to asthma in the last decades. There is now overwhelming evidence showing that this approach is associated with a significant reduction in daily and nighttime symptoms and exacerbations and with better lung function and less BHR.³ Moreover, significant improvement in asthma control has been reported in therapeutic trials in which the dose of ICS was tailored to and increased in direct proportion to the degree of BHR,⁴ sputum eosinophilia,⁵ or exhaled nitric oxide levels,⁶ all noninvasive markers of airway inflammation. These results thus suggest that the clinical improvements observed in asthmatic patients treated with ICSs are most likely attributable to the capacity of these compounds to control airway inflammation.

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AIRWAY INFLAMMATION AND AIRWAY REMODELING: CAUSE AND EFFECT?

Concomitantly with these paradigm-shifting findings, epidemiologic and clinical studies provided strong evidence suggesting that persistent asthma was associated with both deficits in lung function growth⁷ and chronic pathologic changes in the airways. These changes are characterized by an increase in airway smooth muscle mass, subepithelial fibrosis with thickening of the lamina reticularis, mucus gland hyperplasia, and increased vascularity.⁸ Although the intensity of these features of asthma (the so-called airway remodeling) is extremely variable and does not always correlate with the functional changes, there is consensus that airway remodeling contributes to the severity and chronic expression of the disease. This has been supported by cogent studies in genetically modified mice in which overexpression of inflammatory mediators causes airway changes that mimic those observed in human asthma.⁹ Mathematic modeling also suggests that in these experimental studies in mice, airway dysfunction is the result of airway remodeling.⁹

The natural corollary of the concept of asthma as an inflammatory disease was thus that the same processes that underlie the expression of asthma symptoms also determine the chronic changes in airway structure and lung function that are characteristic of the disease. Although this conclusion was supported by studies showing decreased vascularity¹⁰ and reduction in subepithelial fibrosis¹¹ during treatment with ICSs, several lines of evidence suggested that the issues at stake could be more complex. Subepithelial fibrosis, for example, does not correlate with disease duration or with severity of airway inflammation,¹² nor does the degree of vascularity observed directly in the airway with a bronchovideoscope.¹³ Moreover, no studies are available in which markers of airway remodeling were assessed after discontinuation of ICSs, and it is thus not known whether modulation of subepithelial fibrosis and vascularity by ICSs persists beyond the treatment period.

LUNG FUNCTION GROWTH AND DECLINE IN ASTHMA

Perhaps the greatest challenge to the concept that ICSs might prevent the long-term effects of asthma on airway anatomy and physiology came from longitudinal studies of lung function growth and decrease in asthma. Cohort studies from general populations reproducibly concluded that in children with persistent asthma symptoms, most deficits in lung function growth have already occurred by age 6 to 9 years,¹⁴ with a modest further effect of asthma on lung function thereafter. Moreover, although one study suggested that adults with asthma do experience accelerated decrease in lung function,¹⁵ a more recent and longer follow-up of more than 9000 subjects in Busselton, Australia, showed that this is mainly observed among smokers, with asthmatic nonsmokers showing only a 3.7 mL/y additional decrease in FEV₁ when compared with values in nonasthmatic

nonsmokers.¹⁶ These inconsistencies and information gaps notwithstanding, 2 retrospective nonrandomized studies in schoolchildren with asthma¹⁷ and in a general population sample of adults¹⁸ suggested that early introduction of ICSs could indeed prevent deficits in lung function growth and decay, respectively. It was thus quite justified to attempt randomized studies on the use of ICSs in children and adults with the specific objective of assessing their role in the prevention of lung function loss.

INHALED CORTICOSTEROIDS AND ASTHMA PREVENTION

A first such study in schoolchildren, the Childhood Asthma Management Program (CAMP) study,³ was among the initial studies funded by the NHLBI as part of the Asthma Networks. In the CAMP study approximately 1000 schoolchildren aged 5 to 12 years with mild-to-moderate asthma were randomized to daily treatment with budesonide, nedocromil, or placebo taken for a period of 4 to 6 years. The main outcome variable was postbronchodilator FEV₁. Two main results emerged from this study: first, no deficits in mean lung function growth were observed in any of the 3 groups, and second, the budesonide group showed significant improvement in postbronchodilator FEV₁ values at the beginning of the trial compared with that seen in the other treatment arms, but these differences tended to decrease with time and became nonsignificant at the end of the trial. The authors concluded that introduction of ICSs during the school years did not influence lung function growth in children with asthma. More recently, O'Byrne et al¹⁹ assessed the potential role of 3 years of treatment with an ICS (budesonide) in preventing an accelerated rate of decrease in FEV₁ values in adults recently given diagnoses of asthma. The authors concluded that when compared with placebo, budesonide slightly reduced losses of lung function by the end of the trial. However, as was the case for the CAMP trial, the improvements in FEV₁ among patients treated with budesonide occurred during the first 6 weeks of the trial. Subsequently, patients in both arms showed very small decreases in lung function (budesonide, 0.7% decrease per year; placebo, 0.4% decrease per year). As a consequence, there was less difference between arms at the end of the trial than after 6 weeks of treatment. Thus the results of these trials did not support the conclusion that treatment with ICSs blocked the progressive loss of lung function in asthma in schoolchildren and young adults. In addition, very minimal deficits in lung function growth or excess decreases in FEV₁ in children and adults, respectively, were observed.

There are several potential explanations for these findings. It is possible that the children and adults included in these trials might not have had severe enough asthma and therefore might not have experienced the deficits in lung function that perhaps occur in patients with more severe disease. Covar et al,²⁰ reanalyzing data from the CAMP study quoted earlier, have provided a quite convincing answer to this objection. They identified among

the children enrolled in that study those who showed apparent significant deficits in lung function growth during the 4- to 6-year follow-up period and found that both children treated with ICSs and those treated with placebo were equally represented in this group. Thus apparent deficits in lung function growth were insensitive to prolonged ICS treatment. A second explanation could be that the purportedly nonreversible deficits in lung function associated with lung remodeling occur early in life and precede the establishment of asthma as a persistent disease. There is strong support for this hypothesis from epidemiologic cohort studies, which have shown that children who will have persistent asthma enter the school years with deficits in lung function that do not usually worsen with age, even among those with the most frequent disease manifestations.¹⁴ It was thus plausible to surmise that the factors that determine lung remodeling and potentially related changes in lung function could be active during the preschool years, a time at which a high proportion of children who will have asthma show the first clinical manifestations of the disease.

To test this hypothesis, the NHLBI Childhood Asthma Research and Education network, established in 1999 to study unaddressed issues in childhood asthma care, conducted the Prevention of Early Asthma in Kids (PEAK) trial. In the PEAK trial 285 children aged 2 to 3 years at high risk for asthma were randomized to therapy with either an ICS (fluticasone, 88 µg twice daily for 2 years) or masked placebo.²¹ Treatments were interrupted at the end of the 2-year period, and the primary outcome (asthma control days) was measured during the third observational year. Results showed significantly better clinical outcomes and lung function outcomes in children treated with fluticasone than in those treated with placebo. However, clinical differences between groups rapidly disappeared a few weeks after discontinuation of regular treatments, as did functional differences by the end of the trial. Two other recently reported trials in the United Kingdom and Denmark, respectively, used different modalities from those chosen in the PEAK trial to treat with ICSs children who had what appeared to be the first manifestations of asthma during the first 3 years of life.^{22,23} These trials reached the same conclusion as the PEAK trial: very early treatment of asthma with ICSs, even before the persistent form of the disease has become predominant, does not change the natural clinical course of the disease, nor does it affect the level of lung function attained at the end of follow-up.

SYMPTOM-RELATED INFLAMMATION IS NOT RESPONSIBLE FOR DEFICITS IN LUNG FUNCTION IN ASTHMA

Taken together, the data strongly suggest that ICSs, although very effective in controlling asthma symptoms, cannot block or reverse either the deficits in lung function observed in some patients with asthma or the changes in airway structure (presumably “airway remodeling”) that underlie these deficits.

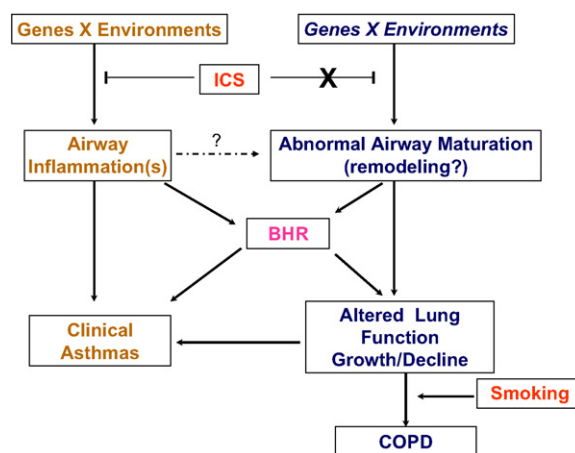


FIG 1. Hypothetical representation of 2 separate developmental pathways present in persistent asthma, one sensitive (*left side*) and the other insensitive (*right side*) to ICSs. These pathways would determine ongoing symptom-related inflammation and deficits in lung function growth and potentially “airway remodeling,” respectively. Both pathways can influence the measured level of BHR during childhood. *COPD*, Chronic obstructive pulmonary disease.

One possible explanation for these unexpected findings is that deficits in airway function (and perhaps airway remodeling) in asthma occur in parallel to and are not the result of ICS-sensitive, symptom-related airway inflammation (Fig 1).²⁴ This contention is supported by the lack of a clear association between markers of airway remodeling, such as subepithelial fibrosis, and the duration and severity of disease (see above). Further support comes from longitudinal studies in which it was demonstrated that BHR was associated with growth of FEV₁ values independently from current asthma symptoms.²⁵ In the study by Xuan et al,²⁵ for example, the attained FEV₁ level at age 19 years was 12% lower in a child who had BHR during the whole study period (eg, from ages 8-10 to 19 years) than in a child who did not have persistent BHR, and this was independent of initial FEV₁ levels and of reported wheezing during the same period. Instead, independent of BHR, children who had reported wheezing during the whole study period had only 3% lower FEV₁ values than those who did not report wheezing during the same period. More recently, Fong et al²⁶ reported that BHR measured at age 6 years was a strong determinant of the FEV₁/forced vital capacity ratio attained by age 22 years, independent of initial lung function and concomitant wheezing. These results thus strongly suggest that a “constitutional” form of BHR detected during the early school years is a strong determinant of the future pattern of growth of airway function, and this determinant might or might not express itself as subsequent wheezing during childhood, perhaps depending on the coexistence of ICS-sensitive inflammatory processes in the airways.

CONCLUSIONS: THE NEXT STEPS

The pioneering trials performed as part of the NHLBI Asthma Networks have quite conclusively shown that

among children with asthma (or at risk for asthma) of different ages, controller therapy with ICSs is efficacious in controlling asthma symptoms but does not change the natural clinical course of the disease. These findings open a series of new, important, and still unaddressed issues in childhood asthma:

- There is a pressing need to develop therapeutic modalities that, initiated even earlier in life and before the development of the first asthma-like symptoms, will prevent the initiation of the disease process that will subsequently result in the parallel pathways of asthma symptoms and chronic airway dysfunction.
- If the existence of a group of children with asthma in whom the disease is effectively progressive is confirmed, early genetic and phenotypic markers are needed to identify these children and to target them for the development of specific therapies that will thwart that progression.
- It is essential to determine whether in children with mild persistent asthma, intermittent, symptom-triggered anti-inflammatory therapy might be as effective as daily continuous therapy with ICSs and other controllers in preventing asthma exacerbations and improving quality of life.

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