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Original article

Association of symptom control with changes in lung function, bronchial hyperresponsiveness, and exhaled nitric oxide after inhaled corticosteroid treatment in children with asthma

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Abbreviations:
ICS, inhaled corticosteroid; BHR, bronchial hyperresponsiveness; eNO, exhaled nitric oxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FEF25−75%, forced expiratory flow at 25−75% of forced vital capacity; AMP, adenosine 5-monophosphate; C-ACT, childhood asthma control test; ACQ, asthma control questionnaire

ABSTRACT

Background: A key therapeutic approach to asthma, which is characterized by chronic airway inflammation, is inhaled corticosteroid (ICS). This study evaluated the association of symptom control with changes in lung function, bronchial hyperresponsiveness (BHR), and exhaled nitric oxide (eNO) after ICS treatment in asthmatic children.

Methods: A total of 33 children aged between 5 and 12 years with mild to moderate persistent asthma were treated with 160 μg ciclesonide per day for 3 months. At days 0 and 90, the following parameters were assessed: asthma symptom scores; lung function, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25−75% of forced vital capacity ($FEF_{25-75\%}$); BHR to methacholine and adenosine 5-monophosphate (AMP); and eNO.

Results: Asthma symptom scores, lung function parameters, BHR to methacholine and AMP, and eNO levels at day 90 were significantly improved versus day 0 (all $p < 0.001$). Symptom scores at day 90 were not correlated with changes in lung function and BHR to methacholine during the follow-up period, whereas those at day 90 were more closely correlated with changes in BHR to AMP ($r = 0.511$, $p = 0.003$) than with eNO ($r = -0.373$, $p = 0.035$). Additionally, changes in PC_{20} AMP were correlated with changes in PC_{20} methacholine ($r = 0.451$, $p = 0.011$) and eNO ($r = -0.474$, $p = 0.006$).

Conclusions: Changes in the BHR to AMP, and to a lesser extent eNO, correlate with asthma symptom control after ICS treatment. BHR to AMP may better reflect the relationship between improved airway inflammation due to ICS treatment and asthma symptoms.

Introduction

Asthma involves chronic airway inflammation characterized by bronchial hyperresponsiveness (BHR) and reversible airway obstruction. Therefore, treatment with anti-inflammatory agents, such as inhaled corticosteroid (ICS), represents the main effective therapy for asthma management. Current guidelines on asthma management adhere to the concept that treatment should aim to reduce or prevent airway inflammation with ICS and that adjustments of the ICS dose for treatment are guided solely by symptoms and lung function.[1] However, the current stepwise strategy for symptom and lung function optimization does not lead to proper control of asthma in all patients.[2] Moreover, in patients with asthma that is considered to be under control, airway inflammation can persist[3–5] and such abnormalities can cause airway remodeling and reductions in lung function during the long-term follow-up period.[6] Therefore, objective evaluation of airway inflammation and its consequences, as well as the evaluation of symptoms, is needed to achieve proper asthma control.

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Many studies have tried to use BHR or inflammation markers as objective markers of the effects of ICS.[2,7,8] It is generally accepted that airway inflammation contributes to the presence and severity of BHR, but reports of a direct association between airway inflammation and BHR have varied according to the method used to measure BHR.[5,9,10] Several studies have shown that BHR to adenosine 5-monophosphate (AMP), an indirect stimulus, is an earlier and more sensitive indicator of the effects of ICS than BHR to methacholine, a direct stimulus.[11–14] In addition, exhaled nitric oxide (eNO) reflects airway inflammation, and changes in eNO after ICS are rapid and reproducible,[15–17] although eNO levels seem to be affected by several factors.[18–22]

However, there is little information to simultaneously relate these objective makers, including BHR to direct or indirect stimuli and airway inflammation markers, to asthma symptom control during ICS treatment in children with asthma. Accordingly, the present study aimed to evaluate the association of symptom scores with changes in lung function, BHR to methacholine or AMP, and eNO after ICS treatment in children with asthma.

Methods

Subjects and study design

A series of 33 children with mild to moderate persistent asthma, aged 5–12 years, was recruited from August to October 2012 from the Childhood Asthma Atopy Center at Asan Medical Center Children's Hospital. All subjects met the following criteria: airway reversibility to β_2-agonist $\geq$12% of the predicted forced expiratory volume in one second (FEV_1) and/or symptom relief using a bronchodilator, a history of recurrent wheezing and/or dyspnea within the previous 12 months, and no severe comorbidities, including bronchiolitis obliterans, malignancy, and congenital heart disease affecting lung function. Before treatment with ICS, all patients were (by design) responsive to methacholine (provocative concentration causing a 20% fall in FEV_1, $PC_{20} \leq 25$ mg/mL) and AMP ($PC_{20} \leq 400$ mg/mL). Definition of disease severity was based on the criteria set in the National Asthma Education and Prevention Program (NAEPP) guidelines.[1]

All subjects were treated with 160-μg ciclesonide per day (Alvesco®, Takeda Pharmaceuticals, Dubendorf, Switzerland) for 3 months, which was administrated with or without a spacer (Vortex®, PARI GmbH, Starnberg, Germany) that was fitted to the mouthpiece, depending on the patient age and inhaler performance. At both days 0 and 90, the following parameters were assessed: asthma symptom scores; lung function, including forced expiratory volume in one second (FEV_1), forced vital capacity (FVC), and forced expiratory flow at 25%–75% of forced vital capacity ($FEF_{25-75\%}$); BHR to methacholine and AMP; and levels of eNO.

The study protocol was approved by the Institutional Review Board of the Asan Medical Center and all participants gave written informed consent after receiving a detailed explanation of the study.

Measurements of lung function and BHR

Basal lung function, including measurements of the FEV_1, FVC, and $FEF_{25-75\%}$, and two bronchial provocation test with methacholine and AMP were performed in all subjects on the same day. The value of the FEV_1 and $FEF_{25-75\%}$ were expressed as a percentage of the predicted value for the global lung function 2012 equations.[23] After methacholine challenge, an AMP challenge was carried out after recovery of the FEV_1 to within 5% of the baseline FEV_1 of a methacholine challenge. Antihistamines, bronchodilators, and other medications were not taken for 48 h before testing on days 0 and 90. ICS administration was stopped for 14 days before testing at day 0, but was continued at day 90.

Methacholine and AMP were prepared in 0.9% saline solution at concentrations of 0.625–25 mg/mL for methacholine (0.625, 1.25, 2.5, 5, 10, and 25 mg/mL) and 3.125–400 mg/mL for AMP (3.125, 6.25, 12.5, 50, 100, 200, and 400 mg/mL). The FVC and FEV_1 values were measured at 1 and 3 min in the methacholine and AMP tests after each administration. The challenge was terminated if FEV_1 dropped by >20% from post-saline value or if maximal concentration of methacholine or AMP was administered. PC_{20} was calculated by linear interpolation of the log-dose-response curves.

Measurements of eNO levels

The eNO fraction was measured using a Niox Mino device (Aerocrine, Solna, Sweden) using a previously described method before bronchial provocation test.[24]

Asthma control assessments

We modified a previous questionnaire for assessing asthma symptom scores.[25,26] Patients were asked to recall their symptoms during the previous month at each visit, and symptom scores included wheezing, use of a short-acting bronchodilator, shortness of breath, nocturnal symptoms, activity limitation, and overall asthma control. All six questions were scored on a 5-point scale, and a high score indicated good asthma control.

Measurements of atopy

A skin prick test (SPT) was performed with 31 common allergens using standard methods[27]: *Dermatophagoides pteronyssinus*, *D. farinae*, *Alternaria*, *Aspergillus*, *Cladosporium*, *Penicillium*, grasses, trees, weeds, ragweed, mugwort, oak, beech, nettle, willow, elm, pine, hop, elder, hazel, oats, lambs quarter, ash, alder, birch, timothy, rye grass, dog, cat, and cockroach. SPT was included a positive control (histamine) and a negative control (isotonic saline). A positive on SPT was defined as a mean wheal diameter of $\geq$3 mm and greater than that of the histamine. Atopy was defined as positive SPT result to at least one allergen.

Total serum IgE and blood eosinophils

Total serum IgE levels were measured with immunoCAP system (Phadia AB, Uppsala, Sweden). Blood eosinophil counts were measured using an automated blood analyzer.

Statistical analyses

Data are presented as means ± SD or as geometric means with a range of 1 SD. Levels of total IgE, blood eosinophil counts, PC_{20} methacholine, PC_{20} AMP, and eNO were log-transformed prior to analysis to normalize the distribution or these values. Variables were then compared using the paired *t*-test, and frequencies were compared using the χ^2 test. Correlations between variables were analyzed using Pearson's correlation test. Changes in PC_{20} methacholine and PC_{20} AMP after 3 months of ICS treatment versus pretreatment values were expressed as dose shifts (in doubling doses) using the following formula: $\Delta\log_{10}PC_{20} = [\log_{10}(PC_{20}$ after the treatment) $- \log_{10}(PC_{20}$ before the treatment)]/$\log_{10}2$.[28,29] A p-value of 0.05 or less was considered to be significant. The SPSS version 19 software package was used for these analyses (SPSS Inc., Chicago, IL, USA).