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The influence of inhaled corticosteroid discontinuation in children with well-controlled asthma

Shengkun Zheng, MD, Qiying Yu, MD, Xiangyan Zeng, MD, Wangming Sun, MD, Yan Sun, MD, Mengrong Li, MD*

Abstract

Asthma is a chronic inflammatory disease that requires adherence to both preventative and therapeutic interventions in disease management. Children with asthma are likely to discontinue inhaled corticosteroids (ICS), especially when symptoms are under control. We aimed to investigate the impact of ICS adherence in children whose symptoms were under control.

The study is cohort study; 35 children with controlled asthma that had undergone 3 years of follow-up were included. Serum eosinophil count, serum total IgE (tIgE), and lung function (FEV1, FEV1/FVC, PEF, FEF20–75%, and PC20) were evaluated at the beginning and end of the follow-up.

At baseline, patients in both the adherent and nonadherent groups were similar. After 3 years, the nonadherent group who had discontinued ICS had a decrease in FEV1 ($P < .05$), FEV1/FVC ($P < .05$), PEF ($P < .05$), and FEF20–75% ($P < .05$). The nonadherent group had no significant improvement in PC20 compared with their values at the beginning of the follow-up, whereas the adherent group had improvement in PC20. Furthermore, there was an increase in serum eosinophil ($P < .001$) and tIgE ($P < .05$) in the nonadherent compared with the adherent group.

Despite good asthma control, airway hyperresponsiveness (AHR) was detected in a large proportion of children with asthma. ICS discontinuation affected lung function, serum eosinophil count, tIgE, and AHR. Adequate adherence is important in asthma management. The benefits of ICS and the influence of drug discontinuation despite good asthma control may encourage better adherence from patients.

Abbreviations: AHR = airway hyperresponsiveness, BHR = bronchial hyperresponsiveness, CI = confidence interval, GINA = Global Initiative for Asthma, ICS = inhaled corticosteroids, tIgE = total immunoglobulin E.

Keywords: airway hyperresponsiveness, asthma, inhaled corticosteroids, PC20

1. Introduction

Asthma is a chronic inflammatory disease characterized by recurrent episodes of chest tightness and cough. Asthma is usually associated with mucus hypersecretion, variable airflow obstruction, and bronchial (airway) hyperresponsiveness (BHR or AHR).[1] Asthma is the most common chronic lower respiratory disease in children, and the prevalence of asthma has recently increased in many countries.[1,2] Despite effective therapies, asthma control is far from optimal in a large proportion of asthmatics worldwide.[3] Medication regimens for asthma management are particularly vulnerable to adherence problems because of chronic need, periods of symptom remission, and the frequent need for multiple medications that are typically inhaled.[4] Children with asthma may cease their inhaled corticosteroids (ICS), especially when their symptoms are under control.

Poor management of childhood asthma is associated with reduced lung function in young adults. One explanation for reduced lung function is inadequate suppression of inflammation. Chronic inflammation plays a key role in the asthma process.[5] Persistent inflammation is associated with airway remodeling and may result in AHR.[1,6] AHR is a risk factor for a decline in lung function.[7] The long-term outcome for a patient with asthma depends on the severity of disease in early life; persistence of asthma into adulthood is more likely in children with more severe airway obstruction and AHR.[7]

ICS are used frequently to treat asthma, suppress airway inflammation, and improve lung function and symptoms.[8,9] Numerous studies have demonstrated the effectiveness of ICS in managing acute and chronic asthma. The Childhood Asthma Management Program (CAMP)[10] and the Regular Therapy (START) in early asthma study[11] found that ICS improved prebronchodilator FEV1 compared with placebo, suggesting improvement in lung function. To reduce or prevent the irreversible component of airflow obstruction, international guidelines recommend early, long-term anti-inflammatory treatment, and emphasize regular treatment of the underlying inflammatory process in asthma.[1,12] However, most patients have poor adherence to asthma medicine, especially ICS.[13,14]

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Department of Pediatrics, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, Wenzhou, Zhejiang, P.R. China.

* Correspondence: Mengrong Li, Department of Pediatrics, The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, 109 West Xueyuan Road, Wenzhou, Zhejiang 325027, P.R. China (e-mail: lmrjohn@163.com).

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Several studies have shown persisting inflammation in the airways of patients who have clinical remission of asthma and in well-controlled asthmatic patients despite treatment with ICS.[7] Therefore, it could be reasoned that asthmatic children with inadequate symptom perception and residual AHR are especially at risk of a decline in lung function.

Numerous studies have focused on how to control asthma. However, less attention has been paid to patients whose symptoms are under control. For patients with well-controlled asthma, patient compliance may decrease. The aim of the present study was to explore whether withdrawal of ICS influenced lung function and airway responsiveness in children with controlled asthma. In this study, we report the clinical results of 35 pediatric patients with well-controlled asthma. We retrospectively evaluated the clinical characteristics and laboratory parameters of these patients, including FEV1, FEV1/FVC, PC20, PEF, FEF20–75%, blood eosinophil count, and serum IgE.

2. Materials and methods

The present study is cohort study; we retrospectively analyzed the medical records of 140 consecutive pediatric patients referred to The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University, China between June 2012 and July 2013. Children 8 to 11 years old who experienced 3 years of follow-up (n = 35) were enrolled in this study. Based on the Global Initiative for Asthma (GINA) guidelines, all 35 participants fulfilled criteria for persistent mild asthma under control.[12] All patients were under good control with ICS and their main food was rice. We contacted the patients every 3 months to ask the parents if their children had had ICS treatment according to the doctor and recorded the ICS withdraw dose during the 3 months. Patients were divided into 2 groups according to their adherence: adherent group, without ICS withdrawn during 3-year follow-up (n = 15), and nonadherent group, ICS withdrawn during 3-year follow-up (n = 20; accumulated ICS withdrawn dose was 0.1980 mg [0.1307–0.2653 mg] during 3 years). Blood was collected to measure blood eosinophil count and serum total immunoglobulin (tIgE) both at the beginning and end of the follow-up period. Lung function, including FEV1, FEV1/FVC, PEF, FEF20–75%, and PC20 were measured. The study was approved by the Ethical Committee of the University Hospital. Written informed consent was obtained from the parents of each participant.

2.1. Immunological parameters

Blood samples were collected to measure serum tIgE levels by antibody assays. The analyses were performed using fluoroimmunoassay technique (UniCAP, Pharmacia Diagnostics, Uppsala, Sweden) in our central laboratory. Serum tIgE levels were determined with an upper limit of 5000 kU/L and a limit of detection of 2 kU/L. Results are presented in kilounits per liter (kU/L).

2.2. Blood eosinophil in serum

Absolute blood eosinophil counts were measured with an automatic cytoanalyzer (Mindray, Shenzhen, China). The normal value of blood eosinophil testing is $\leq 0.45 \times 10^9$ L^{-1}.

2.3. Measurements of pulmonary function and airway responsiveness

With a JAEGER MasterScope Body automated system, pulmonary function tests were obtained as a percentage of predicted values, including FEV1, FEV1/FVC, PEF, and FEF20–75%. Pulmonary function tests in children occurred at least 24 hours after the last use of inhaled short-acting bronchodilator. Airway responsiveness to methacholine was examined in subjects with predicted FEV1 >80%. The provocation concentration of methacholine that produced a 20% decrease in FEV1 (PC20), a representation of airway responsiveness, was calculated. The provocative doses that were used to elicit a positive result were 12.8, 6.4, and 1.6 μmol/L, respectively.

2.4. Statistical analysis

A total of 35 study participants were divided into 2 groups (adherent and nonadherent) based on whether or not they arbitrarily discontinued treatment with ICS during the 3-year follow-up period. The Kolmogorov-Smirnov test was used to evaluate data parameters for normal distribution. Data were reported as the arithmetic mean and 95% confidence interval (CI). Between-group comparison tests were performed using 2-sided *t* tests. PC20 was a categorical variable which has 4 categories: 0, 1, 2, or 3. A value of 0 was considered a negative PC20 test, whereas a value of 1, 2, or 3 was considered positive. The values 1, 2, and 3 represented provocation concentration of 12.8, 6.4, and 1.6 μmol/L, respectively. Between-group categorical variables were compared using χ^2 tests. Numerical data, including FEV1, FEV1/FVC, PEF, FEF20–75%, serum tIgE, and blood eosinophil counts, were compared with a nonparametric Mann-Whitney *U* test. A rank sum test was used to evaluate the difference in PC20 after follow-up in both groups. For all tests, a 2-sided $P < .05$ was considered statistically significant. All analyses were performed using SPSS version 18.0 computer software (Chicago, IL).

3. Results

3.1. Study population and basic characteristics

Between June 2012 and July 2013, 140 children were referred to The Second Affiliated Hospital & Yuying Children's Hospital of Wenzhou Medical University. Thirty-five children (mean age 8.0 ± 3.0 years; 32 males and 3 females) met the criteria previously outlined and were included in the study. All patients were using ICS to control their asthma symptoms. Only 35 patients went through 3-year follow-up (we contacted our patients every 3 month) while others did not. There were 15 patients who were adherent to ICS and 20 patients who were nonadherent. The comparison of the children's characteristics in the 2 groups is summarized in Table 1. At baseline, the patients in both groups were similar except with respect to age, with the adherent group being almost 1 year younger on average than the nonadherent group. There were no significant differences between the adherent and nonadherent groups in terms of serum tIgE, blood eosinophil count, FEV1, FEV1/FVC, FEF20–75%, or PC20 at baseline.

3.2. Lung function and AHR

Studies have shown that ICS can improve lung function and decrease AHR.[8,9] First, we explored the influence of ICS discontinuation on asthma control in children. As shown in Figure 1A, the nonadherent group had a significant decrease in FEV1 compared with the adherent group, indicating that ICS discontinuation affects lung function. Consistent with decreased FEV1, the nonadherent group had lower FEV1/FVC (Fig. 1B) and PEF levels (Fig. 1C) compared with the adherent group.

Table 1

Characteristics of patients with drug nonadherent and adherent.

Characteristics	Obedience		*P* value
	Nonadherent	Adherent	
Age, y*	8.6 (7.4–9.7)	9.9 (8.1–11.6)	.175
Male/female, n	18/2	14/1	1.000
Height, cm*	128.25 (121.09–135.41)	133.43 (124.97–141.90)	.328
Weight, kg*	27.98 (23.85–32.10)	30.47 (25.31–35.63)	.425
BMI, kg/m^{2*}	16.62 (15.71–17.53)	16.70 (15.65–17.74)	.903
Serum tIgE level, kU/L*	811.73 (504.96–1118.51)	759.20 (346.58–1171.82)	.826
Blood eosinophil count, cells $\times 10^9$ L^{-1*}	0.572 (0.396–0.748)	0.532 (0.352–0.712)	.742
FEV1% pred, %*	99.0 (93.8–104.2)	98.3 (92.8–103.9)	.857
FEV1/FVC% pred, %	102.93 (99.19–106.67)	106.15 (102.37–109.93)	.304
PEF% pred, %*	99.5 (90.5–108.5)	93.0 (85.5–100.5)	.271
FEF20–75% % pred, %*	98.1 (88.0–108.2)	92.6 (82.1–103.0)	.433
PD20 class (0/1/2/3), n	7/2/7/4	3/2/6/4	.412

BMI = body mass index, tIgE = total immunoglobulin.
* Mean (95% CI).

FEF20–75% (Fig. 1D) is also an important parameter in the evaluation of asthma. The nonadherent group was found to have lower FEF20–75% compared with the adherent group. These results suggest that despite having good control over asthma symptoms, discontinuing ICS may influence lung function. PC20 indicates airway responsiveness. As shown in Table 2, the nonadherent group had no significant improvement in PC20 compared with the beginning of the follow-up period, whereas

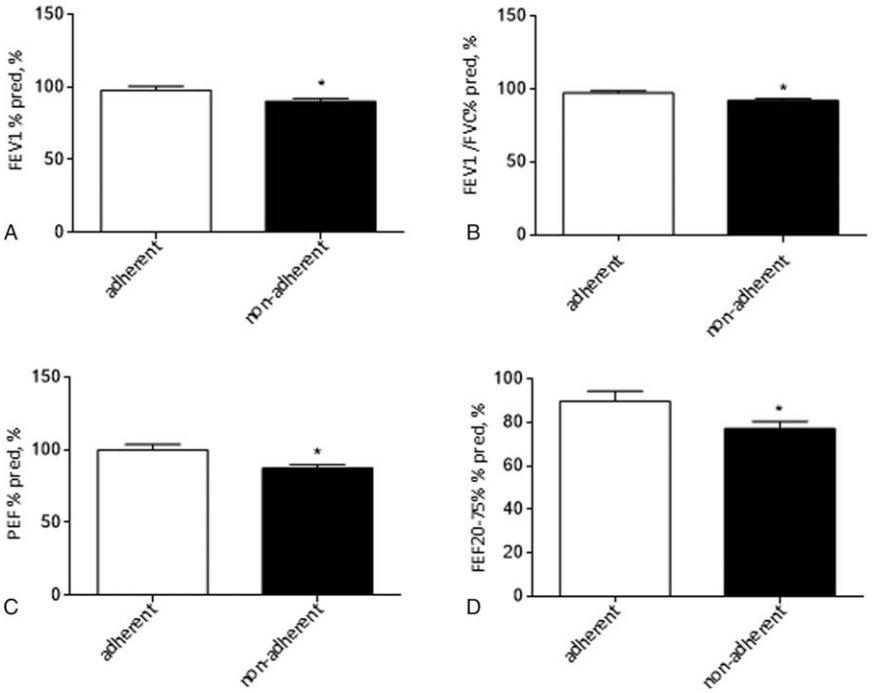

Figure 1. Lung function of adherent and nonadherent group after 3 y follow-up. Notes: Asthma patients under good control with ICS went through 3 y follow-up. At the end of 3 y follow-up, the lung function of the patients was detected, including FEV1% (A), FEV1/FVC% (B), PEF (C), and FEF20–75% (D) (*$P < .05$, vs adherent group). ICS = inhaled corticosteroids.

Table 2

Variation of PC20 in patients after follow-up.

	Total		Nonadherent		Adherent	
	PC20 (positive/negative), n	PC20 class (0/1/2/3), n	PC20 (positive/ negative), n	PC20 class (0/1/2/3), n	PC20 (positive/ negative), n	PC20 class (0/1/2/3), n
Before follow-up	25/10	10/8/13/4	13/7	7/4/7/2	12/3	3/4/6/2
After follow-up	12/23	23/6/3/3	9/11	11/5/2/2	3/12	12/1/1/1
P value	.002	.004	.204	.190	.001	.004

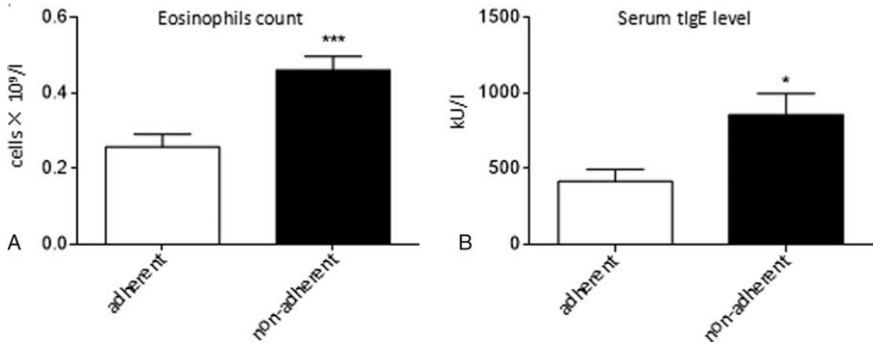

Figure 2. Blood eosinophil count and serum tIgE level of the patients in adherent and nonadherent group. Notes: Asthma patients under good control with ICS went through 3 y follow-up. At the end of 3 y follow-up, blood eosinophil count (A) and serum tIgE level (B) were detect ($^{*}P < .05$, $^{***}P < .001$ vs adherent group). ICS = inhaled corticosteroids, tIgE = total immunoglobulin.

the adherent group exhibited better PC20 on average after follow-up, indicating a role of ICS in attenuating AHR.

3.3. Blood eosinophil count

Blood eosinophils are associated with corticosteroid-responsive asthma.[15,16] We explored the influence of ICS discontinuation on serum eosinophil count. As shown in Figure 2A, there was a significant increase in eosinophils in the nonadherent group compared with the adherent group. ICS discontinuation may affect blood eosinophil count, which may affect asthma prognosis.

3.4. Serum total immunoglobulin E

Total IgE plays a significant role in the process of asthma.[5] There was a significant increase in tIgE in the nonadherent group compared with adherent group (Fig. 2B). This indicates that ICS discontinuation may be associated with asthma deterioration.

4. Discussion

Well-controlled asthma can be defined as optimal pulmonary function, few to no acute exacerbations, minimal or no symptoms, and the ability to enjoy normal activities.[12] Asthma is a chronic inflammatory disease that requires adherence to both preventative and therapeutic interventions to achieve disease control. There are multiple factors that can lead to adherence problems, including the duration of disease, periods of symptom remission, and the need to use multiple (often inhaled) medications. In this study, we focused on children whose symptoms were well controlled. We found that even with well-controlled asthma, the cessation of ICS might impact serum eosinophil count, tIgE, and lung function, as measured by FEV1, FEV1/FVC, PEF, FEF20–75%, and PC20. Thus, optimal medication adherence (eg, taking medication as prescribed by a physician) is important to maximize the benefits of therapy.[17]

However, as for present study there were several limitations. The number of participants was small. Each patient group was even smaller when broken into adherent versus nonadherent. In addition, the patient age range is very small and could also be interpreted as a limitation. Furthermore, pulmonary function tests can vary greatly even among the same patient depending on technique and other factors.

Chronic inflammation is considered central to the pathophysiology of asthma. Several studies have shown persistent inflammation in the airways of patients in clinical remission from asthma and in well-controlled asthmatic patients despite treatment with ICS.[7] Inadequate suppression of airway inflammation is considered a vital factor for those with poor asthma control. Nuijsink et al[7] demonstrated that compared with a symptom-driven strategy, a treatment strategy guided by AHR provides better maintenance of lung function in children with moderate to severe asthma. Children with asthma who received 2 years of asthma treatment guided by airway responsiveness had improved lung function compared with children who were treated based on international guidelines designed around symptoms.[18] These data indicate that not only symptoms, but also monitoring inflammation and lung function are important. Therefore, in addition to controlling symptoms, preservation of lung function in childhood may offer substantial long-term benefits.

Studies have demonstrated peripheral blood eosinophil levels to be associated with asthma severity.[15,16] Eosinophils are principal effector cells of allergic asthma that differentiate from myeloid precursor cells in response to granulocyte macrophage colony-stimulating factor and interleukin (IL)-3.[16] Peripheral blood eosinophil count correlates with the degree of airflow limitation, the severity of symptoms, and airway responsiveness to both direct and indirect bronchial challenge testing.[16] Additionally, the recruitment and activation of eosinophils by IL-13, IL-4, and IL-5 are vital to the pathogenesis of asthma.[16] An increase in blood eosinophil count reflects the severity of asthma. In the present study, the group of patients that was nonadherent with ICS treatment had higher blood eosinophil numbers and decreased lung function, reflected by FEV1, FEV1/FVC, PEF, and FEF20–75%, despite having asthma that was symptomatically controlled. This suggests that ICS discontinuation affects the process of asthma.

Caregivers of asthmatic patients with high tIgE had increased macrophage expression of TLR4 in induced sputum, suggesting that high tIgE is associated with inflammation.[19] In the present study, the patients who were nonadherent to ICS had increased tIgE, suggesting ICS cessation can affect the process of asthma.

A major challenge for physicians in treating those with asthma is noncompliance on the part of patients (and in the case of pediatrics, with patients' parents) with recommendations given by the physician. There are many factors that influence adherence. Among these reasons, concerns about the adverse effects of ICS may have a major influence on attitude and behavior during asthma management. Corsico et al demonstrated a significant inverse relationship between having fear of adverse medication effects and adherence to therapy; this notion is

particularly applicable to asthma treatment. However, the fear of side effects from ICS may be ameliorated by educating patients and their parents on the benefits of adhering to therapy and through providing evidence-based information.[4] Several studies have shown that many of the factors affecting adherence can be overcome by frequent contact with patients, highlighting the importance of frequently reviewing and reinforcing the partnership between patients and health care professionals.[4] Exploration, education, follow-up, and reminders can help to build a trusting relationship and reinforce partnership between patients and health care professionals. This relationship is the prerequisite for success in treating any chronic disease.[20]

In conclusion, we analyzed the effects of ICS discontinuation on asthma control in children. The data revealed that cessation of ICS leads to significantly decrease in FEV1, FEV1/FVC, PEF, FEF20–75%, and PC20, as well as to increases in serum neutrophil and IgE levels. Adherence is a problem in asthma management, but the benefits of the available medicines and the influence of drug discontinuation may encourage adherence in some patients. All parents and children should be educated about asthma treatment and warned to not arbitrarily stop treatment without approval from the physician who established the management plan.

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