Original Article

Low Variability in Peak Expiratory Flow Predicts Successful Inhaled Corticosteroid Step-Down in Adults with Asthma

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What is already known about this topic? Factors predictive of long-term disease control that can be evaluated before the initiation of asthma treatment or at dose reduction of inhaled corticosteroids are unknown.

What does this article add to our knowledge? Low serum IL-33, high serum IL-10, and low variability in peak expiratory flow over 1 week are useful for predicting long-term disease control in adults with asthma after 50% reduction of the daily inhaled corticosteroid dose.

How does this study impact current management guidelines? Serum cytokines such as IL-33 and thymic stromal lymphopoietin may be biomarkers that are predictive of the success of reduced inhaled corticosteroid treatment in adults with asthma.

BACKGROUND: The prognosis for patients beyond 1 year after reduction of their inhaled corticosteroid (ICS) dose remains unknown. Predictive factors that can be evaluated before the initiation of asthma treatment or at ICS dose reduction are unknown.

METHODS: We prospectively studied 223 patients in 6 hospitals in the National Hospital Organization of Japan during the 36 months after 50% reduction of their daily ICS dose. All patients recorded their morning and evening peak expiratory flows (PEFs) in their diaries. Lung function, bronchial hyperresponsiveness, fractional nitric oxide levels, number of eosinophils in sputum, and serum IgE levels were measured in most patients. Serum levels of IL-10, IL-33, and thymic stromal lymphopoietin before ICS dose reduction were measured in all patients.

RESULTS: During the 36-month study period, asthma control was retained in 127 (59.6%) of the 213 enrolled patients who underwent ICS dose reduction. Multivariate logistic regression analysis revealed that, at the initiation of dose reduction, the factors most predictive of maintenance of asthma control after ICS dose reduction were a low serum IL-33 level ($P < .01$), low PEF variability over 1 week ($P = .014$), childhood onset of asthma (at age <10 years) ($P = .03$), and low serum IL-10 level ($P = .035$).

CONCLUSIONS: We demonstrated that low PEF variability over 1 week, high serum IL-10 level, and low serum IL-33 concentration were useful factors for predicting that an adult's asthma will remain in control for months to years after a 50% reduction in the daily ICS dose. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: *Adult asthma; Airway hyperresponsiveness; Asthma management; ICS; Step-down; Innate immunity; Regulatory T cell; IL-10; IL-33*

Current guidelines from the Global Initiative for Asthma (GINA) recommend that when control in adults with asthma is maintained for at least 3 months, treatment can be stepped down to minimize the cost and maximize the safety of the treatment.[1] Asthma management in adult patients can be achieved by combining low-, medium-, or high-dose inhaled corticosteroids (ICSs) with a short-acting β_2-agonist (SABA)[2] and by

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Abbreviations used
ACh- Acetylcholine dichloride
FENO- Fractional exhaled nitric oxide
GINA- Global Initiative for Asthma
Hist- Histamine dihydrochloride
ICS- Inhaled corticosteroid
LABA- Long-acting β_2-agonist
PC_{20}- Provocation concentration causing a 20% fall in FEV_1
PEF- Peak expiratory flow
SABA- Short-acting β_2-agonist
TSLP- Thymic stromal lymphopoietin

monitoring fractional exhaled nitric oxide (FENO),[3] induced sputum eosinophil count,[4] bronchial hyperresponsiveness,[4] and the morbidity score[2] (which includes clinical symptoms of asthma). However, previous studies[3,4] have monitored clinical outcomes for only 1 to 6 months after ICS dose reduction, and the prognosis for patients beyond 1 year after ICS dose reduction remains unknown. In fact, some reports indicate that reducing the ICS dose leads to deterioration of asthma control in adult patients.[5] Moreover, factors that can be evaluated before the initiation of any asthma treatment or at the time of ICS dose reduction and that are predictive of long-term control, such as various biomarkers related to type 2 cytokines or innate immunity, are unknown. We previously reported that 50 of 90 patients (55.6%) who had had no clinical symptoms of asthma for at least 6 months before ICS dose reduction experienced no loss of control thereafter.[6] Factors predictive of success in maintaining asthma control after ICS dose reduction were a relatively low acetylcholine dichloride (ACh) level, decrease of more than 20% (provocation concentration causing a 20% fall in FEV_1 [PC_{20}]) in FEV_1, prolonged (ie, $\geq$6 months) absence of clinical symptoms before ICS dose reduction, low FENO, and a high FEV_1 (%predicted).[6] However, this earlier study evaluated only a small population and was performed at a single center. Here, we prospectively assessed adults with asthma whose ICS doses were decreased by 50%, and we analyzed clinical symptoms and serum biomarkers associated with maintenance of asthma control during a multicenter trial of the National Hospital Organization of Japan.

METHODS

Patients

Between September 2012 and September 2013, we recruited 223 adult patients from 6 National Hospital Organization hospitals in Japan. These patients were diagnosed with moderate or severe asthma according to the American Thoracic Society criteria[7] but had not had any clinical symptoms of asthma for at least 6 months. Asthma severity was assessed according to the current GINA guidelines[1] and thus was classified as follows: step 1, intermittent disease; step 2, mild persistent; step 3, moderate persistent; or step 4, severe persistent. Exclusion criteria included pulmonary diseases other than asthma (eg, chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and bronchiectasis) and eosinophilic lung diseases (eg, allergic bronchopulmonary mycosis and eosinophilic granulomatosis with polyangiitis). The Ethics Committee of our hospital approved the study, and written informed consent was obtained from all patients themselves or from their legal representatives. The ethics approval number was H25-0312001 at the National Hospital Organization and No. 4 in 2012 at the National Hospital Organization Sagamihara Hospital.

Study design

We prospectively evaluated adults with asthma receiving 50% reduced daily doses of ICS and analyzed markers indicative of maintenance of control of asthma in a multicenter trial of the National Hospital Organization of Japan. All patients had been assessed as having asthma of step 2 or greater severity, and all were receiving ICS therapy at study recruitment, but none had shown any clinical symptoms of asthma in the preceding 6 months. Through medical examination and review of logs of self-reported symptoms and patients' diaries, we confirmed that all patients were currently free of clinical symptoms without the use of SABAs and had been for at least 6 months. Patients monitored daytime symptoms including wheezing and expiratory dyspnea, nighttime awakenings due to asthma, the rescue use of metered-dose inhalers, and emergency room visits due to losses of disease control. In addition, we confirmed that all patients had recorded their morning and evening peak expiratory flows (PEFs) in their diaries.

At the beginning of the study, the daily ICS dose was tapered to 50%, but patients remained on the same drug(s), with no change in particle size or device. For patients who used combination inhalers that included a long-acting β_2-agonist (LABA) in addition to ICS, such as budesonide-formoterol combination inhalers, the LABA dose was also decreased by 50%. Patients continued taking all other medications, such as theophylline, leukotriene receptor antagonists, and long-acting muscarinic antagonists, as prescribed before the study. We prospectively studied all patients every 2 to 3 months during the 36 months after the start of ICS dose reduction by reviewing their self-recorded symptoms and PEFs, assessing the use of SABAs, and performing medical examinations. The primary outcome measure was clinical symptoms. Loss of control of asthma was defined as the occurrence of symptoms more than once a week, or the patient's use of inhaled SABAs more than once each week, or restriction of a person's activities (including exercise), or a decrease in FEV_1 or PEF (%predicted) to less than 80% of the predicted value, or a greater than 20% variability in PEF within 1 week.[1] When necessary, patients who experienced a loss of asthma control returned to the daily ICS dose that they had been using before the start of the study; they also received short-term systemic corticosteroids or LABAs or SABAs as needed.

Measured parameters

Variability in PEF over 1 week. Every morning and evening before taking their ICS dose, patients monitored and recorded their PEFs, which had an error of less than 10% variance among each set of 3 PEF measurements. To calculate the PEF variability, we noted the lowest and highest prebronchodilator PEFs (as percentages of the predicted value) obtained within a 1-week test period. The PEF variability within a 1-week test period (%) was calculated as ([maximum PEF − minimum PEF]/maximum PEF × 100%); we calculated this value for each of the 4 weeks before a medical examination.[8]

FENO. FENO levels were measured for 10 seconds at a flow rate of 45 to 55 mL/s by using NIOX Mino (Aerocrine, Solna, Sweden) or at a flow rate of 50 mL/s by using an NO chemiluminescence analyzer (NOA model 280A; GE Sievers Instruments, Boulder, Colo) as an online or offline method, depending on the hospital. Exhaled air measured by using the offline method was collected by