

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 high 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 2018;6:972-9)

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

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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

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
PC₂₀-Provocation concentration causing a 20% fall in FEV₁
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 score² (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 FEV₁ [PC₂₀]) in FEV₁, prolonged (ie, ≥ 6 months) absence of clinical symptoms before ICS dose reduction, low FENO, and a high FEV₁ (%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 criteria⁷ but had not had any clinical symptoms of asthma for at least 6 months. Asthma severity was assessed according to the current GINA guidelines¹ 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 FEV₁ 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 $[(\text{maximum PEF} - \text{minimum PEF}) / \text{maximum PEF} \times 100\%]$; 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

using a Sievers bag collection kit as described previously.⁹ Briefly, subjects took a deep breath of room air through the NO scavenging filter and exhaled through a mouthpiece at a flow rate of 70 mL/s against an expiratory resistance of 10 cm H₂O; 5 seconds later, the exhaled air was collected into the 1.5 L Mylar balloon bag provided in the kit. The collected exhaled air was stored at room temperature and the NO concentration measured within 12 hours. Air was drawn out of the balloons bag at 200 mL/min into an NO chemiluminescence analyzer (NOA model 280A; GE Sievers Instruments) with a response time of 200 milliseconds. FENO values measured by using this method differ by no more than about 20% from the values measured by using online methods.⁹ We confirmed the comparability of the FENO values by using several methods, and the FENO values obtained by using the offline methods were converted into the equivalent FENO values as measured by using NIOX Mino.¹⁰

Eosinophils in sputum. For patients at Sagamihara Hospital, eosinophils in noninduced sputum were quantified by using the Hansel classification system at the first hospital visit and before beginning ICS therapy.¹¹ The eosinophil content of sputum was scored under microscopy as follows: 0, none; 1, rare (1 in scattered fields); 2, few (small numbers in scattered fields); 3, mild (moderate numbers in scattered fields); 4, moderate (~10 per field in multiple fields); and 5, severe (10 or more in all fields), with cell distribution consistent throughout all fields (400×) for scores of 0 and 1 and variable between fields for scores of 2 through 5, with the score assigned according to the highest cell count found in more than 10 fields. This system of scoring corresponds as follows to the percentages of eosinophils as a proportion of total cell count commonly reported elsewhere: score 0, 0%; 1, 1.2% ± 0.2%; 2, 12.7% ± 2.0%; 3, 25.2% ± 1.3%; 4, 44.8% ± 2.1%; and 5, 79.3% ± 1.3%.¹²

Total IgE level. Several enzymatic assays that use anti-IgE antibodies have supplanted the traditional radioallergosorbent test¹³; for example, we measured total IgE levels in serum (IU/mL) by using a radioimmunosorbent test. In addition, antigen-specific IgE (IU/mL) level for 6 different allergens (house dust mite [indicated *Dermatophagoides pteronyssinus*, *Dermatophagoides farina*, or mix], cat, dog, *Alternaria tenuis*, *Aspergillus fumigatus*, and ragweed) was measured by automated immunonephelometry (BN II; Dade Behring, Deerfield, Ill). Atopy was defined as the presence of at least 1 positive antigen with a radioallergosorbent test score of 1 (ie, 0.35 IU/mL).

Bronchial hyperresponsiveness to ACh and histamine dihydrochloride. Provocation tests with ACh (Ovisot, Daiichi Pharmaceutical, Tokyo, Japan) or histamine dihydrochloride (Hist; Sigma, St Louis, Mo) were performed on separate days (with at least 7 days between tests) within 1 month after the first hospital visit at the time of diagnosis and at reduction of ICS dose. All patients were treated with antiasthma drugs such as SABAs or sustained-release theophylline before ICS treatment within 1 month after the first hospital visit.

We performed inhalation testing by using a modified version of the method recommended by the American Thoracic Society.¹⁴ All antiasthma medications were withheld for at least 12 hours before the provocation test. We prepared ACh at 0.157, 0.313, 0.625, 1.25, 2.5, 5, 10, and 20 mg/mL and Hist at 0.078, 0.157, 0.313, 0.625, 1.25, 2.5, 5, and 10 mg/mL by dilution in PBS (pH 7.4). After each inhalation, FEV₁ was measured by using a spirometer

(Auto Spiro AS-303; Minato Medical Science, Osaka, Japan). Subjects first inhaled isotonic saline, as a control, and then ACh or Hist aerosol from a nebulizer (model 646; DeVilbiss, Somerset, Pa) by tidal breathing for 2 minutes. The operating airflow of this device was 5 L/min. Patients with an FEV₁ of less than 1.00 L or showing a decrease of more than 10% with saline alone were not tested further. Patients then inhaled increasing concentrations of ACh or Hist until FEV₁ fell by more than 20% of its initial postsaline value or until the maximal ACh or Hist concentration was used.

The percentage decrease in FEV₁ from the postsaline value was plotted against the log concentration of inhaled ACh or Hist. Bronchial sensitivity was expressed as the provocative concentration of the agonist causing a decrease of more than 20% (PC₂₀) in FEV₁. At the end of the test, any residual decrease in FEV₁ was reversed through the inhalation of salbutamol (0.5 mL of a 5 mg/mL solution). Subjects with an AChPC₂₀ of less than 20 mg/mL or a HistPC₂₀ of less than 10 mg/mL were defined as having positive bronchial hyperresponsiveness.

Serum IL-10, IL-33, and thymic stromal lymphopoietin levels. Before ICS reduction, serum levels of IL-10, IL-33, and thymic stromal lymphopoietin (TSLP) were assayed by using the appropriate ELISA kit for each of the human cytokines (eBioscience, San Diego, Calif). Briefly, triplicate plates were coated with capture antibody overnight at 4°C, washed 3 times, and blocked for 1 hour with 1× assay diluent. Plates were washed 3 times and incubated with IL-10 or TSLP standards and unknown samples for 2 hours at 4°C, or with IL-33 standards and unknown samples overnight at 4°C. Plates were washed 3 times and incubated with detection antibody for 1 hour at room temperature. Plates were washed 3 times, incubated with avidin–horseradish peroxidase conjugate for 30 minutes, washed 4 times, and incubated with 100 µL substrate solution for 15 minutes at room temperature; 100 µL stop solution was then added. Absorbance at 450 nm was measured by using an ELISA plate reader.^{15,16}

Statistical analysis

All values are expressed as means ± 1 SD (range) unless otherwise specified. Between-group comparisons were performed by using 2-way ANOVA with repeated measures or the Mann-Whitney *U* test. Multiple logistic regression analysis was used to calculate risk factor coefficients. Related risk factors were identified by using likelihood ratio testing. *P* values of less than .05 were considered statistically significant. All statistical analyses were performed by using StatView version 5.0 software (SAS Institute, Cary, NC).

RESULTS

Of the 223 patients recruited in total, 10 (4.5%) were excluded from the study because they were lost to follow-up (Figure 1). A total of 86 (40.4%) of the 213 enrolled patients who underwent ICS dose reduction experienced loss of control of asthma during the 36-month study period (Figures 1 and 2); the time to the first loss of control (mean ± 1 SD) was 9.5 ± 7.5 months (Figure 2). Univariate analysis showed that patients with a history of childhood onset of asthma were more likely to avoid loss of control of asthma during reduced-dose ICS therapy than to experience loss of control (*P* < .05) (Table I). In addition, the group without loss of asthma control had lower PEF variability over 1 week (*P* < .01) and lower serum IL-33 levels (*P* < .01) than did patients who experienced loss of asthma control (Table I). There were no significant differences

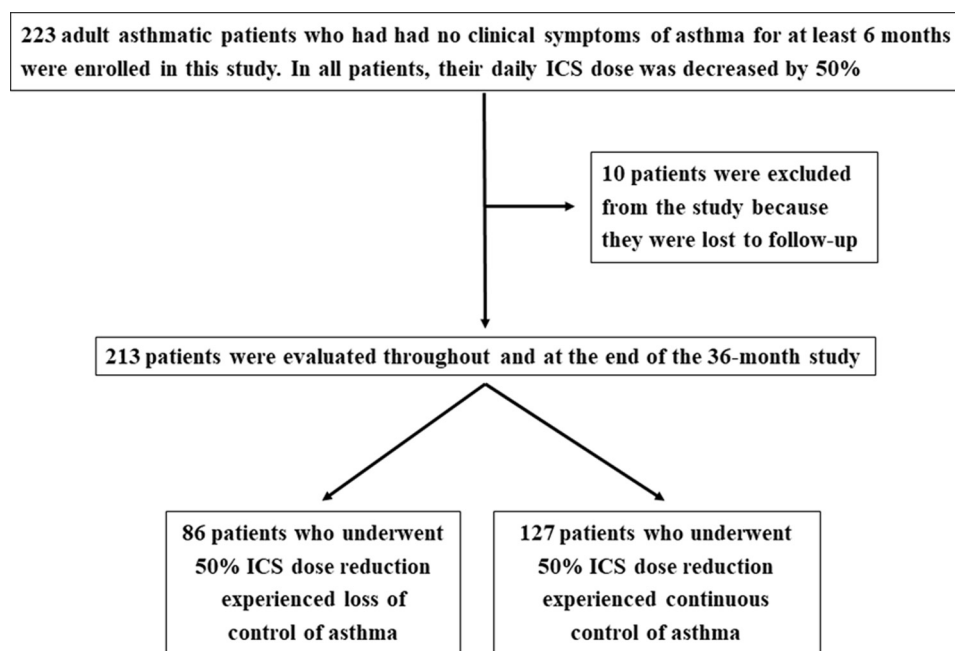


FIGURE 1. Flow diagram illustrating the progress of patients during this study.

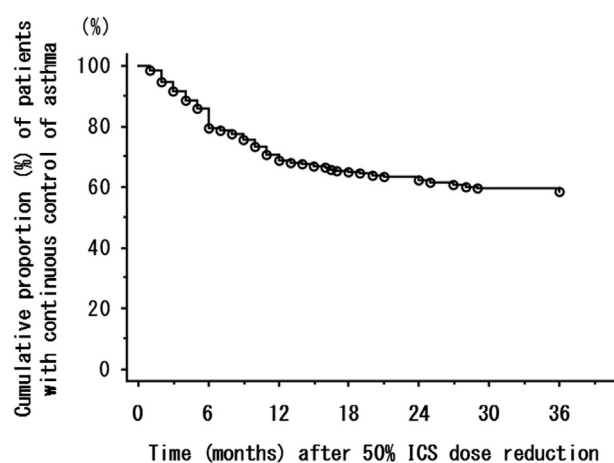


FIGURE 2. Clinical course of adults with asthma after 50% reduction in their daily ICS doses. The Kaplan-Meier plot shows the percentages of patients who maintained asthma control during the 36 months after ICS dose reduction.

between the patient groups in terms of age at entry into the study, sex ratio, age at onset of asthma, duration of asthma, atopy status, or smoking history. Nor were there significant differences between the 2 groups in terms of eosinophils as a percentage of white blood cells, score of eosinophils in sputum, vital capacity, FEV₁, maximum expiratory flow rate at 50% of forced vital capacity, maximum expiratory flow rate at 25% of forced vital capacity, or AChPC₂₀ or HistPC₂₀ at the first hospital visit or at initiation of ICS dose reduction. In addition, neither FENO, serum IL-10, or TSLP level at initiation of ICS dose reduction nor the duration without clinical symptoms differed between groups. Because only a few patients (33 of 213 patients [15.5%])

received ICS only (ie, without a LABA or long-acting muscarinic antagonist) at initiation of ICS dose reduction, we analyzed the influence of ICS-only use on predicting the loss of asthma control after dose reduction in this subpopulation separately. When examining the influence of other medications added to ICS, we included the entire study population in the analysis. There were no significant differences between patient groups regarding the kind of ICS used or the addition of other treatments, such as LABAs, leukotriene receptor antagonists, long-acting muscarinic antagonists, and theophylline.

Regarding patients who used ICS-LABA combinations before reduction of ICS, 81 patients (38.0% of 213 patients) used fluticasone-salmeterol and 52 patients (24.4% of 213 patients) used budesonide-formoterol; the percentage of patients who experienced loss of asthma control did not differ significantly between these 2 groups (46 of the 81 patients [56.8%] who used fluticasone-salmeterol; 33 of the 52 patients [63.5%] who used budesonide-formoterol). Control of asthma did not differ between patients whose LABA dose was reduced compared with those without reduction of LABA dose. Reduction of LABA dose by 50% did not affect loss of control.

Multivariate logistic regression analysis revealed that, at the initiation of dose reduction, the factors most predictive of maintenance of control after ICS reduction were (in descending order) 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 high serum IL-10 level ($P = .035$) (Table II). Age at onset of asthma after age 10 years, daily dose of ICS before ICS dose reduction, duration of absence of clinical symptoms, and FENO at ICS dose reduction were not predictive of duration of asthma control after ICS dose reduction.

We also measured PEF variability at 12 months (in the group of patients without loss of control for 36 months) or at loss of

TABLE I. Univariate analysis of baseline factors predictive of successful ICS dose reduction

Characteristic	Patients without loss of control (n = 127)	Patients with loss of control (n = 86)	Univariate analysis <i>P</i>
Age at study entry (y)	55.3 ± 16.2	57.3 ± 15.0	NS*
Sex (male/female), n	54/73	27/59	NS†
Age at onset of asthma (y)	41.0 ± 19.1	43.4 ± 16.6	NS*
Duration of asthma (from age at onset to study entry) (y)	14.2 ± 14.0	13.8 ± 16.5	NS*
Type of asthma (atopic/nonatopic), n	74/52	50/32	NS†
Smoking history (nonsmoker/ex-smoker/current smoker), n	96/21/10	57/20/9	NS†
Childhood onset of asthma (yes/no), n	29/98	9/77	<.05†
Allergic rhinitis (yes/no), n	70/56	44/41	NS†
Atopic dermatitis (yes/no), n	19/107	8/77	NS†
Family history of asthma (yes/no), n	32/77	17/62	NS†
At first hospital visit			
Stage 1/2/3/4 at severity of asthma (n)‡	0/7/93/27	0/3/60/23	NS†
Log serum total IgE	2.291 ± 0.644	2.255 ± 0.715	NS§
Proportion of eosinophils (%) in WBC	7.2 ± 7.5	6.9 ± 5.3	NS*
Score of eosinophils in sputum (score: ≤2, ≥3), n	30/19	23/10	NS†
VC (predicted %)	102.8 ± 19.2	101.7 ± 20.6	NS*
FEV ₁ (predicted %)	94.1 ± 45.4	84.4 ± 18.8	NS*
V ₅₀ (predicted %)	59.9 ± 28.2	52.1 ± 23.0	NS*
V ₂₅ (predicted %)	45.3 ± 26.2	39.2 ± 21.0	NS*
Change in FEV ₁ after inhalation of β-agonist (mL)	185 ± 157	148 ± 148	NS*
Mean (range) AChPC ₂₀ (μg/mL) (n = 178)	3,443 (322-20,000)	3,622 (430-20,000)	NS§
Mean (range) HistPC ₂₀ (μg/mL) (n = 129)	1,879 (141-10,000)	2,328 (67-10,000)	NS§
ICS therapy before dose reduction			
Time from onset of asthma to initiation of ICS therapy (y)	6.5 ± 10.4	6.4 ± 10.6	NS*
Type of ICS (FP/BUD/BDP-HFA/CIC), n	60/62/5/0	44/38/4/0	NS†
Daily dose of ICS (mg; converted to CFC-BDP equivalent)	1,018.3 ± 532.2	1,169.1 ± 596.2	NS*
Duration of ICS therapy (y)	6.3 ± 6.1	6.3 ± 6.4	NS*
At initiation of ICS dose reduction			
Log serum total IgE	2.204 ± 0.753	2.092 ± 0.731	NS§
Proportion (%) of eosinophils in WBC	4.4 ± 3.5	4.2 ± 2.7	NS*
n (%) receiving ICS only	22 (17.3)	11 (12.8)	NS†
n (%) receiving LABA	95 (74.8)	70 (81.3)	NS†
n (%) receiving LTRA	44 (34.6)	33 (38.4)	NS†
n (%) receiving LAMA	5 (3.9)	3 (3.5)	NS†
n (%) using theophylline	10 (7.9)	6 (7.0)	NS†
FEV ₁ (predicted %)	92.7 ± 17.7	94.7 ± 16.9	NS*
V ₅₀ (predicted %)	78.0 ± 31.8	77.0 ± 28.8	NS*
V ₂₅ (predicted %)	67.5 ± 24.0	59.9 ± 25.7	NS*
Mean (range) AChPC ₂₀ (mg/mL) (n = 184)	13,152 (6,422-20,000)	11,066 (1,088-20,000)	NS§
Mean (range) HistPC ₂₀ (mg/mL) (n = 130)	6,714 (472-10,000)	6,808 (138-10,000)	NS§
FENO (ppb) in all patients¶	27.6 ± 16.3	29.5 ± 17.2	NS*
Length of time without clinical symptoms (mo)	17.5 ± 13.3	15.3 ± 16.9	NS*
PEF variability in 1 wk (%)	7.1 ± 11.2	12.1 ± 14.5	<.01*
Serum IL-10 (pg/mL)	7.6 ± 21.7	5.2 ± 1.6	NS§
Serum IL-33 (pg/mL)	75.6 ± 176.2	142.5 ± 229.8	<.01§
Serum TSLP (pg/mL)	7.9 ± 4.3	7.5 ± 4.2	NS§
During treatment with reduced-dose ICS			
PEF variability over 1 wk (%)#	9.3 ± 6.2	14.5 ± 12.2	<.01*

BDP-HFA, Beclomethasone dipropionate-hydrofluoroalkane; BUD, budesonide; CIC, ciclesonide; FP, fluticasone propionate; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; NS, not significant; VC, vital capacity; V₅₀, maximal expiratory flow rate at 50% of forced vital capacity; V₂₅, maximal expiratory flow rate at 25% of forced vital capacity.

Data are given as means ± 1 SD, where appropriate; *P* values of less than .05 were considered statistically significant.

*Two-way ANOVA with repeated measures between the 2 groups.

†Chi-square testing revealed no significant differences in the values for the 2 groups.

‡According to GINA guidelines.

§Differences between groups were evaluated by using the Mann-Whitney *U* test.

||According to the Hansel classification.

¶FENO values obtained by using the offline method were converted into the equivalent FENO values as measured by using NIOX Mino.

#PEF variability over 1 wk (%) measured at 12 mo in the group without loss of control group, or measured at loss of control in the group with loss of control within 1 mo.

TABLE II. Logistic regression modeling of the baseline factors predictive of long-term asthma control after 50% ICS dose reduction

Variable	Odds ratio	95% CI	P
Age at onset of asthma (y), mean $\pm$ 1 SD	0.997	0.976-1.018	.77
Childhood onset of asthma (at <10 y)	0.282	0.088-0.907	.03*
ICS therapy until reducing the ICS dose			
Daily dose of ICS (μ g; converted to CFC-BDP equivalent)	1.000	0.999-1.000	.48
At reduction of ICS dose			
Duration without clinical symptoms (mo)	1.005	0.982-1.028	.66
PEF variability over 1 wk (%)	0.931	0.879-0.985	.014*
FENO (ppb)	0.978	0.95-1.003	.078
Serum IL-10 level (pg/mL)	1.306	1.018-1.676	.035*
Serum IL-33 level (pg/mL)	0.995	0.993-0.998	<.01†

CFC-BDP, Chlorofluorocarbon-propelled beclomethasone dipropionate aerosol.

* $P < .05$ by logistic regression.

† $P < .01$ by logistic regression.

control (in the group of patients with loss of control within 1 month after the reduction of ICS). PEF variability over 1 week in the without-loss-of-control group was significantly less than that in the with-loss-of-control group ($P < .01$) (Table I).

DISCUSSION

In a recent meta-analysis, the risk of loss of control of asthma in adult patients who decreased their ICS dose by 50% after a symptom-free period of 12 to 24 weeks did not increase during a 4- to 52-week follow-up period¹⁷; in contrast, adults with asthma in another study who maintained their full ICS dose had more symptom-free days than did those with 50% ICS dose reduction.¹⁸ However, because of the relatively short duration of the cited studies, they cannot be considered to be reliable evaluations of the long-term risk of loss of control of asthma after dose reduction.¹⁹ We expect that the findings of our current 36-month study will help to clarify this risk. Guidelines regarding optimal rates of ICS reduction and evaluation intervals have not been established. As presented in the guidelines of the US National Asthma Education and Prevention Program, important indicators of impaired asthma control include nighttime awakening, interference with normal activity, SABA use for symptom control, decline in lung function, and responses indicating impaired asthma control on validated questionnaires.²⁰ Several of these indicators are shared by the GINA guidelines.¹ In our current study, approximately 40% of all subjects experienced loss of asthma control over the 36-month study period, half of those within the first 6 months after ICS dose reduction and approximately 80% during the first year (Figure 2). These results suggest that clinical symptoms or PEF must be closely monitored during the first 12 months after ICS dose reduction.

The GINA guidelines include various step-down strategies for adults with asthma, including decreasing the ICS dose by 25% to 50% and eliminating additional therapeutics such as LABAs and leukotriene receptor antagonists.¹ However, patients using low-dose ICS-LABA combinations who followed the GINA guidelines and stopped their LABA frequently experienced loss of asthma control.²¹ We therefore chose to reduce the ICS dose but to continue all other asthma treatments. Reduction of LABA dose in addition to ICS did not influence control of asthma.

Clinical factors that might be predictive of loss of asthma control after ICS reduction include disease symptoms, lung

function, airway responsiveness, and biomarkers such as eosinophilic inflammation and FENO in the airways. Moreover, potentially predictive biomarkers, such as type 2 cytokines, that might be monitored before the initiation of any asthma treatment or reduction in ICS dose would be valuable tools but currently are unknown. In this regard, various stimuli, such as allergens, promote the release of IL-25, IL-33, and TSLP from lung epithelial cells. These factors, in turn, play a crucial role in driving the T_H2 -mediated immune-inflammatory response, including eosinophilia, because they induce the production of T_H2 -type cytokines (including IL-5) by activated T_H2 lymphocytes and type 2 innate lymphoid cells.^{22,23} In patients with asthma, the concentration of IL-33 in bronchoalveolar lavage fluids is inversely correlated with FEV₁, a measure of airway obstruction.²⁴ Our current results indicate that decreased serum levels of IL-33, but not TSLP, might be predictive of successful asthma control after ICS dose reduction. The serum TSLP level was lower than the serum IL-33 level in our study, perhaps because more types of epithelial cells produce IL-33 than TSLP.

CD4⁺CD25⁺Foxp3⁺ regulatory T cells are central to the maintenance of immune homeostasis and thus are attractive targets for human immunotherapy. Consistent with their anti-inflammatory functions, regulatory T cells produce classic anti-inflammatory cytokines, including IL-10, TGF- β , and IL-35.^{25,26} For example, IL-10 and TGF- β 1 significantly reduce cytokine secretion by type 2 innate lymphoid cells.²⁷ Logistic regression modeling in the current study revealed a high serum IL-10 level as a potentially predictive marker for long-term asthma control after reduction of ICS therapy. By extension, an increased number of regulatory T cells might also be indicative of asthma control after ICS dose reduction. This possibility merits further investigation. Although serum levels of IL-10 and IL-33 were highly indicative of loss of asthma control after ICS reduction, the expense of measuring these cytokines prohibits their use in general practice. In contrast, despite the large variability in the results, PEF monitoring is relatively inexpensive and easy and can be performed daily. Consequently, PEF monitoring is more useful in day-to-day asthma management than is measuring serum cytokines, such as IL-10 and IL-33.

Compared with those with early-onset asthma, patients in whom asthma was diagnosed when they were older than 13 years have more severe disease, with persistent airflow limitation,²⁸ few antigen sensitivities in skin tests, decreased lung function,²⁹ and a

rapid decline in lung function,³⁰ despite having a shorter duration of disease.²⁹ Our patients with childhood onset of asthma tended to retain asthma control after reduction of ICS dose, perhaps because of their less severe disease and more favorable response to ICS treatment than those of patients who became asthmatic when older.

In addition to airway inflammation, airway remodeling is influenced by the duration and severity of asthma³¹ and by levels of serum IgE.³² Measures of lung function, including bronchial hyperresponsiveness testing,³³ and of small-airway impairment (measured as FEV₁, and maximum expiratory flow rate at 50% of forced vital capacity), as well as markers of airway inflammation, such as eosinophils in sputum³⁴ and FENO,³⁵ are useful for monitoring asthma control. However, lung function, bronchial hyperresponsiveness, serum total IgE level, eosinophils in sputum, and FENO did not differ between our 2 groups of patients. We surmise that because most of our enrolled patients were step 3 or 4 and thus had moderate to severe asthma, neither marked airway remodeling nor airway inflammation differed significantly between the loss-of-control and maintenance-of-control groups.

The initial diagnosis of asthma was performed according to GINA guidelines by the pulmonologists at 6 National Hospital Organizations, and the accuracy of this diagnosis may have varied among the individual pulmonologists. Furthermore, except for the information that patients had received ICS for at least 6 months, details regarding the type, dose, and duration of ICS therapy were often unavailable.

In the current study, we confirmed that high PEF variability during the weeks before reduction of ICS dose—rather than a 1-time measure of FEV₁ or maximum expiratory flow rate at 50% of forced vital capacity—is predictive of loss of control of asthma after ICS dose reduction. In addition, bronchodilator responsiveness at the first hospital visit did not suggest future loss of disease control, although we did not repeat this testing at multiple points after ICS dose reduction. We consider that the change in PEF over 1 week reflects the asthma control achieved over several days, whereas a change in FEV₁ after inhaled SABA represents the disease control on that particular day only.

Although PEF monitoring is useful for asthma management, twice-daily measurements indefinitely likely will be burdensome to patients. However, twice-daily PEF monitoring during any particular 1-week period might not accurately reflect the overall PEF variability during the weeks preceding ICS step-down. We therefore recommend ongoing twice-daily measurement of PEF even though individual measurements might occasionally be lost.

Current GINA guidelines suggest to “reduce the ICS dose by 50% and continue the second controller,” to “continue combination ICS–LABA with 50% reduction in the ICS component, by using available formulations,” and that “discontinuing LABA is more likely to lead to deterioration.”¹ In addition, patients who used low-dose ICS–LABA combinations and who stopped their LABA treatment had loss of control of their asthma.²¹ In our current study, patients who used a fluticasone-salmeterol ICS–LABA combination (ie, Adair) underwent 50% dose reduction of the ICS dose only and continued LABA treatment at their current dose. However, patients who used a budesonide-formoterol combination (ie, Symbicort) experienced 50% reductions of both their ICS and LABA doses. This difference reflects the fact

that Advair is marketed in multiple dosage formulations, such as Advair-100, Advair-250, and Advair-500, whereas only a single formulation of Symbicort is available in Japan. For patients taking Symbicort, “ICS reduction” actually involves a decrease in both the ICS and LABA doses; consequently, we confirmed no difference in outcome after dose reduction of ICS only compared with ICS–LABA. Except for those who used Symbicort, all patients had a 50% reduction of the ICS dose only and continued all other medications at current doses.

In summary, we have demonstrated that low variability in PEF over 1 week, high serum IL-10 level, and low serum IL-33 concentration are useful factors for predicting that an adult with asthma will remain in control of the asthma for months to years after a 50% reduction in the daily ICS dose.

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