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ORIGINAL ARTICLE

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Markers for Step-Down of Inhaled Corticosteroid Therapy in Adult Asthmatics

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ABSTRACT

Background: Treatment guidelines recommend the use of inhaled corticosteroids (ICS) as first-line therapy for all stages of persistent asthma. However, it is unknown whether ICS dose reduction in adult asthmatics is compatible with maintaining asthma control. Moreover, there are no predictors of efficacy in maintaining asthma control upon ICS reduction.

Methods: We recruited 90 adult patients with moderate or severe asthma but no clinical symptoms of asthma for at least 6 months. All patients reduced their ICS doses by half but continued taking other asthma-related medications. As a primary outcome, we measured asthma exacerbations during the 12 months following ICS reduction. We also further monitored patients from the above study who had maintained total asthma control for 12 months after ICS reduction and who had continued on their reduced doses of ICS or had further reduced, or stopped, their ICS.

Results: Forty of ninety patients (44.4%) experienced exacerbations after ICS reduction (time to first exacerbation: 6.4 ± 3.6 months). Multivariate logistic regression modeling revealed a rank order of predictors of success in ICS reduction while retaining asthma control: acetylcholine (ACh) PC_{20} ($p < 0.01$); length of time with no clinical symptoms before ICS reduction ($p < 0.01$); FeNO ($p = 0.028$); and forced expiratory volume in 1 s (FEV_1; % predicted) ($p = 0.03$). Finally thirty-nine of 50 patients maintained total asthma control for at least 2 years after the initial ICS reduction.

Conclusions: In asthma patients with normalized $AChPC_{20}$ of 20 mg/mL or 10 mg/mL and no clinical symptoms for at least 12 or 24 months it may be possible to successfully reduce ICS without increasing exacerbations for long time.

KEY WORDS

adult asthma, airway hyperresponsiveness, asthma management, ICS, step-down

INTRODUCTION

Treatment guidelines recommend the use of inhaled corticosteroids (ICS) as first-line therapy for persistent asthma of all severities.[1] Controlled asthma is defined by the Global Initiative for Asthma (GINA) guidelines as no daytime symptoms or limitation of activities, no nocturnal symptoms or awakening, no need for reliever or rescue treatment, and normal lung function (peak expiratory flow or forced expiratory volume in 1 s (FEV_1) > 80% of predicted or personal best). GINA guidelines recommend that, when control is maintained for at least 3 months, treatment can be stepped down to minimize cost and maximize

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the safety of the treatment. For asthma control achieved by medium-to-high daily doses of ICS alone, a 50% reduction in daily dose should be attempted after 3 months of control.[2-4] For control achieved by low-dose ICS alone, most patients may be switched to once-daily dosing.[5,6] For asthma controlled with the combination of ICS and a long-acting β_2-agonist (LABA), the preferred approach is to reduce the daily dose of ICS by approximately 50% while continuing the LABA.[7] Discontinuing LABA too early in controlled asthma in patients treated with ICS and LABA leads to loss of asthma control.[8-10]

It has been reported that asthma management can be achieved by combining increased or decreased inhaled ICS with a short-acting β_2-agonist[11] and by monitoring FeNO,[12-14] induced-sputum eosinophil count,[14-17] bronchial hyperresponsiveness (BHR),[15] or the morbidity score[2] (which includes asthma clinical symptoms). However, these studies[8-10,12,15,16,18-20] monitored clinical outcomes only from 1 to 6 months after ICS reduction. The prognosis remains unknown for patients more than 1 year after stepping down their daily ICS dose. In fact, there are reports that reduction of ICS leads to a deterioration in asthma control in adult patients.[2,10,16,18] Moreover, predictive factors that can be evaluated at the time of ICS reduction, or before the initiation of any asthma treatment, are unknown. Predictors might include clinical symptoms, lung function, airway responsiveness, or biomarkers such as eosinophilic inflammation in the airways.

We previously reported that 47 of 134 adult patients with asthma (35.1%) who did not have symptoms in the 6 months after achieving normalized BHR to acetylcholine (ACh) experienced exacerbations at a mean of 8.0 ± 7.0 months after their daily doses of ICSs were halved.[21] Here, to identify predictors of success in decreasing inhaled ICS without increasing exacerbations in the subsequent 12 months, we prospectively studied adult asthma patients in whom ICS intake was reduced.

METHODS

PATIENTS

Between March 2009 and May 2010, we recruited 90 adult patients at the Clinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara, Kanagawa, Japan, who suffered from moderate or severe asthma and who had not had any clinical symptoms of asthma for at least 6 months. All patients had been diagnosed according to the American Thoracic Society criteria.[22] Asthma severity was assessed according the current GINA guidelines[1] and classified according to those guidelines as: Step 1, intermittent; Step 2, mild persistent; Step 3, moderate persistent; and Step 4, severe persistent. Exclusion criteria included pulmonary diseases other than asthma (chronic obstructive pulmonary disease, interstitial pulmonary fibrosis, and bronchial ectasis) and eosinophilic lung diseases such as allergic bronchopulmonary mycosis and Churg-Strauss syndrome.

STUDY DESIGN

STUDY 1: All recruited patients were receiving ICS therapy but had not had any clinical symptoms for at least 6 months while on therapy. We confirmed that all patients were free of clinical symptoms and had been for at least 6 months by medical examination and review of diaries in which they had recorded their symptoms. Monitored symptoms included daytime symptoms such as a wheeze and expiratory dyspnea, night-time awakenings due to asthma or use of rescue metered-dose inhalers, and emergency room visits due to exacerbations. All patients had their daily ICS doses halved but remained on the same ICS with no change in particle size or device. However, patients continued taking other medications such as theophylline, long-acting β-agonists, leukotriene receptor antagonists (LTRA), and/or anticholinergic agents. We prospectively studied all patients during the 12 months following the ICS reduction by reviewing symptoms they recorded in a diary and by medical examinations every 2 or 3 months. The primary outcome measure was clinical symptoms. An asthma exacerbation was defined as the occurrence of symptoms more than once a week or a need by the patient to use inhaled short acting β-agonists more than twice a month. Symptoms were defined as wheezing and expiratory dyspnea during the day or night-time awakenings due to asthma.[21] If necessary, patients that experienced an exacerbation were placed back on the daily dose of ICS that they had been using before the start of the study and treated with short-term systemic corticosteroids or long- or short-acting β-agonists. Not all patients that experienced exacerbations required hospitalization for an asthma attack.

STUDY 2: We further monitored for another 12 months the prognosis of patients for another 12 months in Study 1 who had maintained total asthma control for 12 months after ICS reduction. These patients were distributed into three groups: 1) patients who continued their halved initial daily ICS dose; 2) patients with severe asthma whose daily ICS dose before the dose halving had been the maximum (1600 μg as chlorofluorocarbon beclometasone dipropionate; CFC-BDP equivalent) and whose daily ICS dose after 12 months was decreased to one-quarter of the initial daily dose; and 3) patients with moderate asthma who, after 12 months, discontinued their halved ICS dose (400 μg CFC-BDP equivalent) completely (Fig. 1).

At the first hospital visit, and before ICS treatment, eosinophils in non-induced sputum were quantified by using the Hansel classification system.[23] The pro-

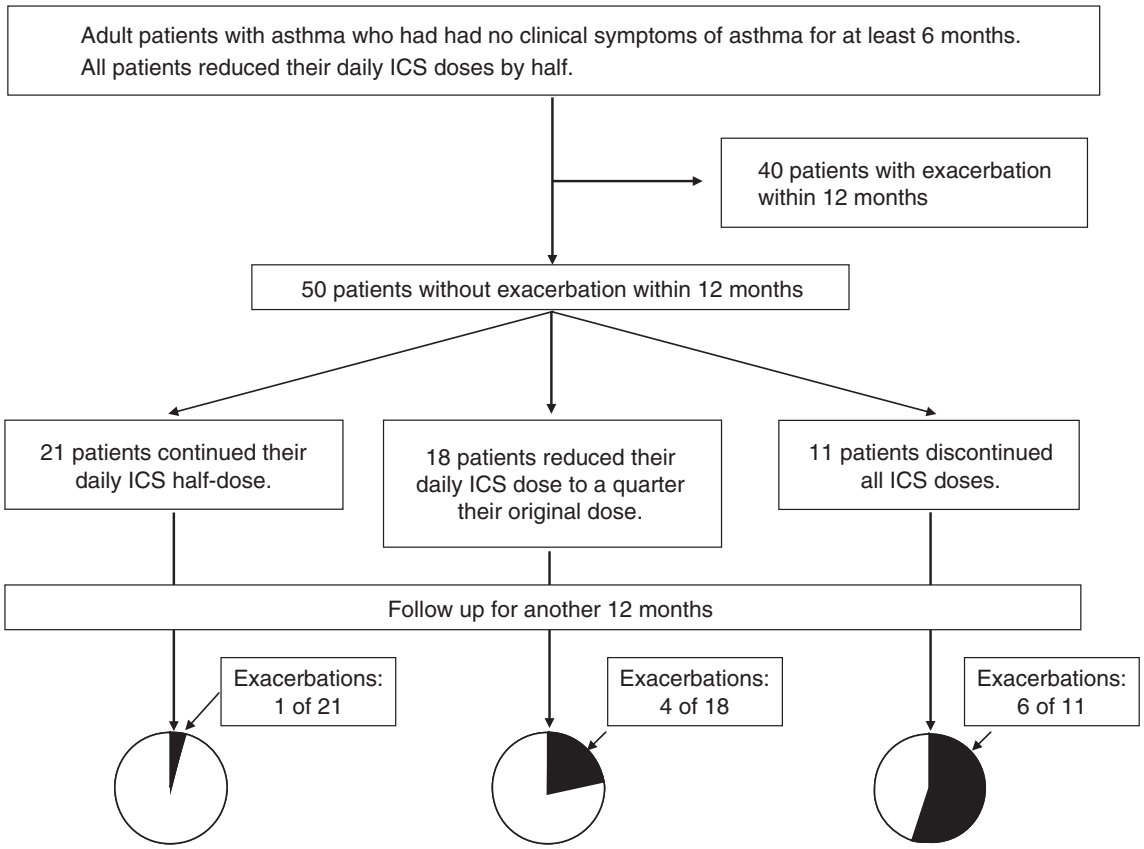

Fig. 1 Protocol and follow-up for patients studied for an additional 12 months after 12 months of reduced daily ICS. Fifty patients who were exacerbation-free 12 months after ICS reduction were distributed into three groups (21 patients continued their daily ICS half-dose, 18 reduced their daily ICS dose to a quarter of the original dose, and 11 discontinued their reduced ICS dose of 400 μg).

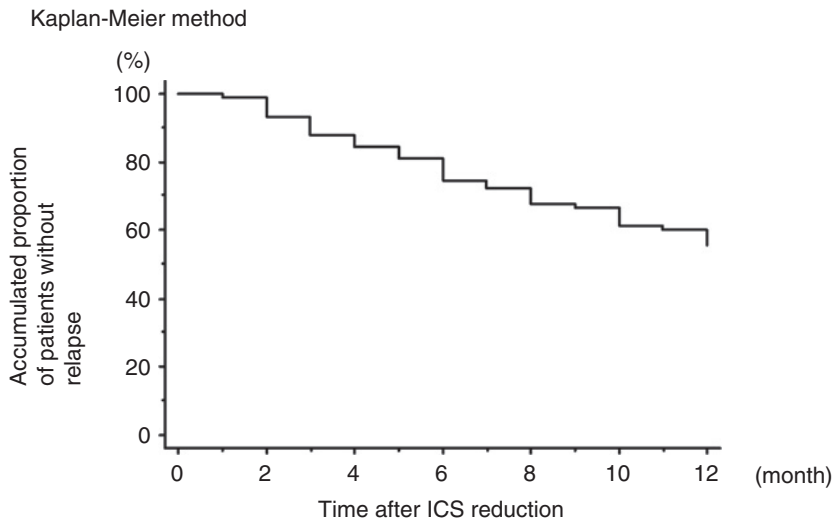

Fig. 2 Clinical courses of patients after ICS reduction. Kaplan-Meier plot of the percentage of patients remaining free of exacerbations. Patients were free of clinical symptoms for at least 6 months before entering the study.

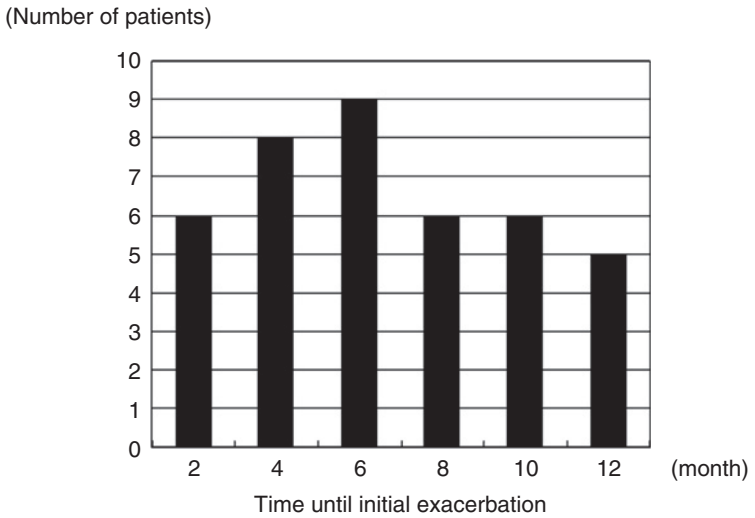

Fig. 3 Time until initial exacerbation. Numbers of patients and times after ICS reduction at which they experienced an initial exacerbation.

portion of eosinophils in whole blood was also measured. Eosinophil amounts in sputum were scored by microscopy as 0 (none), 1 (few; 1 in 1 microscope field), 2 (slight; small numbers in 1 field), 3 (mild; moderate numbers in 1 field), 4 (moderate; many in 1 field), or 5 (severe; many in all fields), with scores of 0 and 1 consistent throughout the entire smear and scores of 2 to 5 verified under high power (400×).

Antigen sensitivity was measured by intracutaneous skin testing.[24] In brief, a 0.05-mL solution of each of six allergens (house dust mite, cat, dog, *Alternaria tenuis*, *Aspergillus fumigatus*, and ragweed) was injected intradermally and the effect judged 15 min after injection. Histamine (0.4 μg) was used as a positive control. Skin reactions were judged positive if they were larger than the histamine reaction. Atopy was defined as a positive intracutaneous skin reaction to at least one antigen.

FeNO was measured (see below) when the daily dose of ICS was reduced. Provocation tests with ACh or histamine (Hist) were performed (see below) on separate days within 1 month after the first hospital visit and at the time of reduction of inhaled ICS. All patients were treated with anti-asthma drugs such as short-acting β_2 agonists or sustained-release theophylline before ICS treatment within one month from the first visit.

The hospital ethics committee approved the study in accordance with the Helsinki Declaration. We obtained written informed consent from each patient.

MEASUREMENT OF BRONCHIAL HYPERRESPONSIVENESS TO ACH AND HIST

We performed inhalation testing using a modified method according to American Thoracic Society (ATS) guidelines.[25] All anti-asthma medications were withheld for at least 12 h before the provocation test. We prepared ACh chloride (Ovisot, Daiichi Pharmaceutical, Tokyo, Japan) at 0.157, 0.316, 0.625, 1.25, 2.5, 5, 10, and 20 mg/mL and Hist dihydrochloride (Sigma, St Louis, MO, USA) at 0.078, 0.157, 0.316, 0.625, 1.25, 2.5, 5, and 10 mg/mL by dilution in buffered saline solution (pH 7.4). FEV_1 was measured with a spirometer (Auto Spiro AS-303, Minato Medical Science, Osaka, Japan) after each inhalation. Subjects inhaled ACh aerosol from a nebulizer (DeVilbiss 646, DeVilbiss, Somerset, PA, USA) by tidal breathing for 2 min. The operating airflow of this device was 5 L/min. Isotonic saline was inhaled first as a control. Patients with FEV_1 <1.00 L or showing a decrease of >10% with saline alone were not tested further. Increasing concentrations of ACh or Hist were then inhaled until FEV_1 fell by >20% of its post-saline value or until the maximum ACh or Hist concentration was reached. The percentage fall in the FEV_1 from the post-saline solution value was plotted against the log concentration of inhaled ACh or Hist. Bronchial sensitivity is expressed as the provocative concentration of the agonist causing a decrease in FEV_1 of >20% (PC_{20}). At the end of the test, any fall in the FEV_1 was reversed by the inhalation of salbutamol (0.5 mL of a 5 mg/mL solution). Subjects with an $AChPC_{20}$ of <20 mg/mL or a $HistPC_{20}$ of <10 mg/mL were defined as having positive BHR.

MEASUREMENT OF FeNO

Exhaled air was collected with a Sievers bag collection kit in accordance with the method reported by Tsuburai *et al*.[26] Briefly, subjects took a deep breath of room air through the NO scavenging filter and exhaled through a mouthpiece with a flow rate of 70 mL/s against an expiratory resistance of 10 cm H_2O; 5 s later, the exhaled air was collected into the 1.5-L Mylar bag provided in the kit. The collected exhaled

Table 1 Baseline factors for patients who were exacerbation-free, or not, in the 12 months following ICS reduction

	Exacerbation-free group $N = 50$	Exacerbation group $N = 40$	p-value
Age at entry of study (y) †	49.1 ± 14.6	50.9 ± 15.9	NS[1]
Sex (M/F)	17/33	15/25	NS[3]
Age at onset of asthma (y) †	34.7 ± 18.0	35.8 ± 20.7	NS[1]
Age at first hospital visit (y) †	41.1 ± 14.7	43.9 ± 15.7	NS[1]
Duration of asthma (from age at onset to entry) †	14.5 ± 10.5	15.2 ± 12.8	NS[1]
Type: atopy/nonatopy	37/13	24/16	NS[3]
Smoking history (non-smoker/ex-smoker + current smoker)	36/14	28/12	NS[3]
At first hospital visit			
Number with step 1/2/3/4 asthma severity ‡	0/0/25/25	0/0/18/22	NS[3]
log IgE RIST in serum †	2.343 ± 0.579	2.325 ± 0.749	NS[2]
Patients with eosinophils (%) in WBC	6.3 ± 4.3	7.0 ± 5.4	NS[1]
Eosinophil score in sputum § (score ≤2, ≥3)	17/13	12/12	NS[3]
VC (predicted, %) †	103.4 ± 17.4	101.0 ± 16.3	NS[1]
FEV_1 (predicted, %) †	85.9 ± 20.8	79.6 ± 21.3	NS[1]
V_{50} (predicted, %) †	57.9 ± 28.5	55.5 ± 29.1	NS[1]
V_{25} (predicted, %) †	50.8 ± 40.1	41.5 ± 23.5	NS[3]
Mean $AChPC_{20}$ (range)(μg/mL)	4852.9 (322-20000)	4508.2 (430-20000)	NS[3]
Mean $HistPC_{20}$ (range) (μg/mL)	1056.8 (141-10000)	946.2 (67-10000)	NS[3]
At ICS reduction			
FEV_1 (predicted, %) †	91.1 ± 15.1	84.1 ± 16.7	<0.05[1]
V_{50} (predicted, %) †	74.3 ± 26.3	68.1 ± 25.9	NS[1]
V_{25} (predicted, %) †	67.5 ± 24.0	59.9 ± 25.7	NS[1]
Mean $AChPC_{20}$ (range)(μg/mL)	17823.8 (6422-20000)	9616.1 (1088-20000)	<0.01[3]
Mean $HistPC_{20}$ (range) (μg/mL)	4375.2 (472-10000)	2157.7 (138-10000)	<0.05[3]
FeNO (ppb) in all patients †	25.6 ± 12.0	43.4 ± 27.3	<0.01[3]
FeNO (ppb) in non-smoking patients †	25.1 ± 12.5	41.4 ± 27.0	<0.01[3]
FeNO (ppb) in ex- or current- smoking patients †	26.7 ± 11.2	47.6 ± 28.8	<0.01[3]
Duration with no clinical symptoms (months) †	15.2 ± 9.4	11.1 ± 6.9	<0.05[3]

† Mean ± standard deviation.

‡ According to GINA guidelines.

§ According to the Hansel classification.

NS, not significant.

[1]Two-way ANOVA with repeated measures among two groups.

[2]Differences between groups were evaluated by using the Mann-Whitney U-test.

[3]Chi-squared testing revealed no significant differences in the values for the two groups.

Values of $p < 0.05$ were considered statistically significant.

air was stored at room temperature and the NO concentration measured within 12 h. The air was drawn out of the balloons at 200 mL/min into an NO chemiluminescence analyzer (NOA model 280A, Sievers Instruments) with a response time of 200 ms. The FeNO measured by this method is consistent with about 80% of the values measured with online methods.[26]

STATISTICAL ANALYSIS

All values are expressed as means ± standard deviation (range) unless otherwise specified. Statistical comparisons between groups were performed by means of a two-way analysis of variance (ANOVA) with repeated measures or with the Mann-Whitney *U*-test. A multiple logistic regression analysis was used to calculate risk factor coefficients. Values of $p < 0.05$ were considered statistically significant. Statistical analysis was performed with StatView v. 5.0 software (SAS Institute; Cary, NC, USA).

RESULTS

STUDY 1: Forty of ninety asthma patients (44.4%) given reduced ICS daily doses experienced asthma exacerbations during the study. The mean time to the first exacerbation was 6.4 ± 3.6 months (Fig. 2). Twenty-three of the forty patients (57.5%) experienced exacerbations sooner than 6 months. The re-

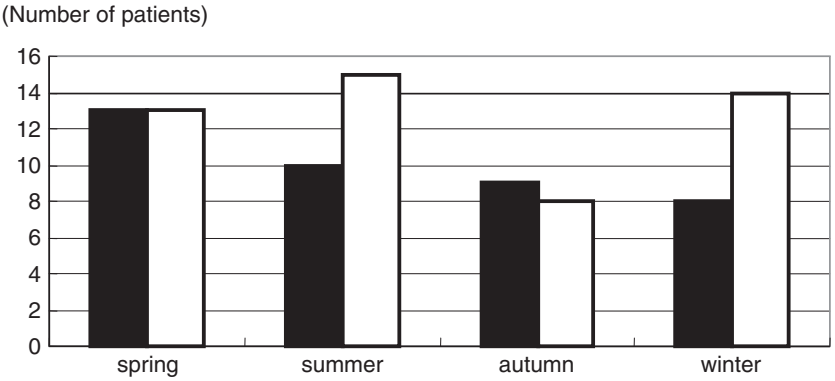

Fig. 4 Season at ICS reduction. Numbers of patients and seasons at the time of ICS reduction. Spring represents March through May, summer June through August, autumn September through November, and winter December through February. Black bars indicate patients with exacerbations. White bars indicate patients without exacerbations.

Table 2 Treatment characteristics before ICS reduction

	Exacerbation-free group $N = 50$	Exacerbation group $N = 40$	p-value
ICS therapy until reduction			
Duration from onset of asthma to initiation of ICS therapy (y) †	7.1 ± 8.0	9.1 ± 11.4	NS[1]
Type of ICS; FP/BUD/BDP-HFA/CIC	22/25/2/1	19/13/7/1	NS[2]
Daily dose of ICS (μg) (converted to CFC-BDP equivalent) †	1172.0 ± 423.8	1130.0 ± 421.4	NS[1]
Duration of ICS therapy (y) †	2.5 ± 2.0	2.3 ± 1.7	NS[1]
At ICS reduction			
Use of LABA; *n* (%)	16 (32.0%)	15 (37.5%)	NS[2]
Use of LTRA; *n* (%)	7 (14.0%)	7 (17.5%)	NS[2]
Use of LAMA; *n* (%)	3 (6.0%)	2 (5.0%)	NS[2]
Use of theophylline; *n* (%)	2 (4.0%)	5 (12.5%)	NS[2]

† Mean ± standard deviation.

NS, not significant; FP, fluticasone propionate; BUD, budesonide; BDP-HFA, beclometasone dipropionate hydrofluoroalkanes; CIC, ciclesonide; LABA, long-acting b agonist; LTRA, leukotriene receptor antagonist; LAMA, long-acting muscarine antagonist.

[1]Two-way ANOVA with repeated measures among two groups.

[2]Chi-squared testing revealed no significant differences in the frequencies of two groups.

Values of $p < 0.05$ were considered statistically significant.

maining patients that experienced exacerbations (42.5%) experienced their first one between 6 and 12 months after their ICS reductions (Fig. 3).

All patients were classified as step 3 or 4 on the basis of the GINA guidelines. For comparison, the patients were grouped into those that had experienced an exacerbation and those that had not (Table 1). There were no significant differences between the patient groups in terms of age at entry into the study, sex ratio, age of onset of asthma, duration of asthma, atopy status, or smoking history. Nor were there significant differences between the two groups in terms of serum IgE level, as measured by using the Radio-ImmunoSorbent Test (RIST), eosinophils as a percentage of WBCs, score of eosinophils in sputum, %VC, FEV_1%, $\%V_{50}$, $\%\dot{V}_{25}$, $AChPC_{20}$, or $HistPC_{20}$ at the first hospital visit. However, upon reduction of inhaled ICS, the group without exacerbations had significantly higher %FEV1 ($p < 0.05$), $AChPC_{20}$ ($p < 0.01$), and $HistPC_{20}$ ($p < 0.05$) and the duration of the period without clinical symptoms was significantly longer ($p < 0.05$). In addition, for all patients and for patients grouped as non-smokers or ex- and current-smokers, FeNO was significantly lower in the exacerbation-free group than in the group with exacerbations (Table 1). There was no effect of the season at ICS reduction on the number of patients with or without exacerbations (Fig. 4). The number of months with no clinical symptoms following ICS reduction was 15.2 ± 9.4 for patients without, and 11.1 ±

Table 3 Logistic regression modeling of baseline factors predictive of the success of ICS reduction

Variable	Exponent	95% confidence interval	*p*-value
Age at asthma onset	0.994	0.946-1.044	0.81
Duration of asthma (from age at onset to entry)	0.987	0.906-1.074	0.75
Type: atopic/nonatopic	0.254	0.062-1.037	0.056
Smoking history (non-smoker/ex- + current smoker)	0.435	0.103-1.833	0.26
ICS therapy until ICS reduction			
Daily dose of ICS	0.999	0.998-1.001	0.40
At ICS reduction			
FEV_1	1.104	1.009-1.207	0.03*
V_{50}	0.956	0.912-1.003	0.068
$AChPC_{20}$	35.1	4.073-30.184	<0.01**
$HistPC_{20}$	2.474	0.466-13.141	0.29
FeNO	0.961	0.927-0.996	0.028*
Length of time with no clinical symptoms before ICS reduction	1.182	1.056-1.323	<0.01**

*$p < 0.05$ by logistic regression, **$p < 0.01$ by logistic regression.

Table 4 Patient characteristics at time of ICS reduction, and percentages of patients with no exacerbations for 1 year after reduction

Characteristics at time of ICS reduction	% with no exacerbations for 1 year
$AChPC_{20}$ >20 mg/mL	75.00
$AChPC_{20}$ >20 mg/mL + time with no clinical symptoms before ICS reduction ≥12 months	86.20
$AChPC_{20}$ >20 mg/mL + time with no clinical symptoms before ICS reduction ≥24 months	89.50
$AChPC_{20}$ >10 mg/mL + time with no clinical symptoms before ICS reduction ≥12 months	73.50
$AChPC_{20}$ >10 mg/mL + time with no clinical symptoms before ICS reduction ≥24 months	81.00
$AChPC_{20}$ >10 mg/mL + FeNO <40 ppb	75.90
$AChPC_{20}$ >10 mg/mL + FeNO <30 ppb	78.60
$AChPC_{20}$ >10 mg/mL + $\%FEV_1$ at ICS reduction >80	71.20
$AChPC_{20}$ >10 mg/mL + $\%FEV_1$ at ICS reduction >90	70.30
$AChPC_{20}$ >10 mg/mL + $\%FEV_1$ at ICS reduction >100	77.80
Time with no clinical symptoms before ICS reduction ≥12 months	64.10
Time with no clinical symptoms before ICS reduction ≥24 months	73.90

6.9 for patients with, exacerbations. However, in both groups, the range for the time to exhibit clinical symptoms was large (6 to 36 months) (Table 1).

The duration from onset of asthma to initiation of ICS therapy, the kind of ICS, the daily dose of ICS, and the duration of ICS therapy did not differ significantly between the two groups. In addition, there were no significant differences between the patient groups in the use of other treatments such as LABA, LTRA, long-acting muscarine antagonist (LAMA), and theophylline (Table 2).

We used a multivariate logistic regression model to determine factors predictive of a lack of exacerbations after ICS reduction. Factors measured at the time of ICS reduction that were most predictive of success were, in order of significance: $AChPC_{20}$ ($p < 0.01$), duration before ICS reduction without clinical symptoms ($p < 0.01$), FeNO ($p = 0.028$), and %FEV1 ($p = 0.03$) (Table 3). The daily dose of ICS before reducing ICS, the $\%V_{50}$, and the $HistPC_{20}$ measured when the ICS dose was reduced, were not predictive.

As described above, normalized $AChPC_{20}$ >20 mg/mL at the time of ICS reduction was the best predictor of an exacerbation-free period over the next 12 months (Table 3). The length of time for which patients were free of asthma symptoms before ICS reduction was the second most effective predictor. For patients with normalized $AChPC_{20}$ of >20 mg/mL or > 10 mg/mL and/or an asthma-free period of at least 12 or 24 months before ICS reduction, we also compared the percentages without any exacerbations within 1 year after ICS reduction (Table 4). For patients with $AChPC_{20}$ >20 mg/mL, the percentage without exacerbations within 1 year of ICS reduction was 75.0%. Among those patients with $AChPC_{20}$ >20 mg/mL and no clinical symptoms for 12 or more

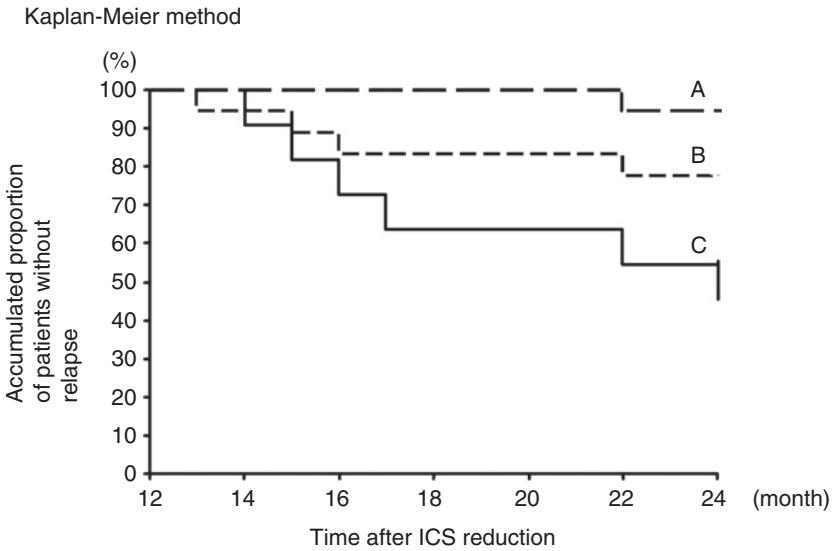

Fig. 5 Clinical courses of patients who continued on the same reduced dose of ICS, were given a further reduction in the dose of ICS, or discontinued ICS. Kaplan-Meier plot of the percentages of patients remaining free of exacerbations. Some patients did not experience exacerbations within 12 months of their initial ICS reduction. Twenty-one of these exacerbation-free patients continued on with their same reduced ICS dose (A). Eighteen continued at an ICS dose that was one-quarter their original dose (B), and 11 patients continued with no ICS (C).

months before ICS reduction, 86.2% remained free of exacerbations for at least 1 year. Moreover, among those patients with $AChPC_{20}$ >20 mg/mL and no clinical symptoms for 24 or more months before ICS reduction, 89.5% were exacerbation-free at 1 year (Table 4). For patients with $AChPC_{20}$ >10 mg/mL at ICS reduction and with no clinical symptoms for 24 or more months before ICS reduction, 81.0% were exacerbation-free. No other clinical factors or combination of factors identified any groups of patients that achieved exacerbation-free percentages of greater than 80%.

STUDY 2: We also analyzed the prognosis of 50 patients from Study 1 who had maintained total asthma control for 12 months after ICS reduction (Fig. 1). Twenty-one of the 50 patients continued therapy beyond 12 months at their half doses of ICS. Twenty of these 21 patients remained exacerbation-free for a mean of 21.5 ± 3.1 months after ICS reduction (Fig. 5). The asthma of 14 of the 18 patients (77.8%) with severe asthma who had been treated with a maximum ICS daily dose of 1600 μg (as chlorofluorocarbon beclometasone dipropionate [CFC-BDP] equivalent) before the first ICS reduction remained controlled for a mean of 11.1 ± 1.6 months after a further dose reduction to a quarter their original daily dose. However, of the 11 patients with moderate asthma who had used an initial daily ICS dose of 800 μg (as CFC-BDP equivalent) before dose reduction to 400 μg and eventually discontinued their ICS entirely, 6 (54.5%) deteriorated at a mean of 4.2 ± 3.6 months after ICS discontinuation (Fig. 5). Thirty-nine of the 50 patients maintained total asthma control for at least 2 years after the initial ICS reduction.

DISCUSSION

It remains difficult to reduce inhaled ICS without promoting subsequent exacerbations, even in adult asthma patients who have achieved normalized BHRs in response to ACh and who have not had asthma symptoms for 6 months.[21] Indeed, our results showed that 44.4% of asthma patients with no clinical symptoms for at least 6 months experienced exacerbations within 1 year after ICS reduction to half the initial daily dose. These findings were independent of the season at ICS reduction. Similarly, reduction of inhaled ICS in patients with their asthma stabilized by intermittent treatment with a combination of ICS and LABA decreases the maximum mid forced expiratory flow after 4 years.[27] There are no published randomized controlled trials of step-down therapy of ICS,[28] and guidelines for the rate of ICS reduction and the interval for evaluation have not been validated. Given the issues described above, and because asthma control may deteriorate at a highly variable rate and intensity, we suggest that reduction of ICS therapy should be gradual. This suggestion is reinforced by our finding that patients in whom the duration of the period without any clinical symptoms before ICS reduction was at least 24 months did not experience ex-

acerbations compared with those in whom the symptom-free period was at least 12 months.

Chronic eosinophilic inflammation in the lower airways may promote airway remodeling.[29-33] Airway remodeling is also influenced by the duration and severity of asthma[34-36] and by levels of serum IgE.[37] Measures of lung function in asthma, including BHR,[38] small airway impairment[1] measured as FEV_1, and V_{50}, as well as markers of airway inflammation such as eosinophils in sputum[39] and FeNO,[40] are useful for monitoring asthma control. Moreover, BHR and airflow limitations interact and are important risk factors for the development of asthma. We reported previously that, in adult patients with severe asthma, BHR induced by ACh is related to the degree of eosinophilic airway inflammation.[36,41] However, BHR induced by Hist indicates airway remodeling, and particularly airway smooth muscle hypertrophy.[36,42] Patients in the group that experienced exacerbations after ICS reduction had a lower initial $HistPC_{20}$ than patients that remained exacerbation-free. These results may reflect greater airway remodeling in the group that had subsequent exacerbations. However, by a multivariate logistic regression model, $AChPC_{20}$, but not $HistPC_{20}$, was the best predictive factor. This result may indicate that patients with less eosinophilic airway inflammation can be treated successfully with ICS reduction and remain exacerbation free for an extended time, even if they have some airway remodeling, such as airway smooth muscle hypertrophy.

Our results showed that the most predictive factors of success in stepping down ICS without subsequent exacerbations were, first, normalized BHR induced by ACh, and second, a history, before ICS reduction, of 24 or more months that were free of asthma symptoms. In addition to $AChPC_{20}$, we evaluated FeNO and FEV_1 as potential predictors of success of ICS reduction. In this study, 26 of 90 patients (28.9%) were ex- or current smokers. We previously reported a higher cutoff point of FeNO in smokers with asthma than in non-smokers.[43] Our data showed that FeNO at the time of ICS reduction was significantly lower in the exacerbation-free group, independent of whether patients were current or ex-smokers. Thus the difference in FeNO may not reflect the effects of smoking.

Our analysis of the initial characteristics of patients who had no exacerbations for at least 12 months after ICS reduction (Table 3) suggested specific factors that could be clinically useful in identifying patients likely to respond well to ICS reduction. The most important factor is normalized $AChPC_{20}$ alone, or in addition to a symptom-free period of 12 or 24 months before ICS reduction. Patients with $AChPC_{20}$ ≥10 mg/mL and free of any clinical symptoms for at least 24 months before ICS reduction also appeared to have fewer exacerbations in the 12-month study period. However, other patient characteristics such as FEV_1 or FeNO before ICS reduction combined with $AChPC_{20}$ ≥10 mg/mL did not define groups with comparable percentages of exacerbation-free patients (Table 3). A symptom-free period of at least 12 or 24 months before ICS reduction was in itself not a predictor of a 12-month exacerbation-free period after reduction.

We analyzed further the prognosis of 50 patients in Study 1 who had maintained total asthma control for 12 months after ICS reduction. Thirty-nine of these patients maintained total asthma control for at least 2 years after their initial ICS reduction. However, most exacerbations in Study 2 patients occurred within 12 months in the group that discontinued all ICS treatment after their initial ICS reduction.

The predictive factors that we identified may be useful in defining asthma patients who would benefit for an extended period of time from ICS reduction. However, the complexities of the clinical response to ICS reduction, as illustrated above, indicate that remission or cure of adult asthma remains difficult and warrants further study.

GINA[1] and Japanese[44] Guidelines recommend treatment protocols to achieve asthma control that are based on a patient's level of asthma control. However, ICS reduction soon after achieving initial control can lead to asthma exacerbations, and repetitive exacerbations may lead to airway remodeling[34,35] or decreased FEV_1.[45] In light of the findings reported here, we recommend that step-down therapy should be performed gradually after patients have been symptom-free for at least 24 months. As a result, the low frequency of exacerbations may suppress airway remodeling, give a good prognosis, and contribute to reduced long-term medical expenses.

In summary, we demonstrated useful factors, such as $AChPC_{20}$, for identifying patients who could remain exacerbation-free for extended periods of time with a reduction in their daily ICS dose. However, the ability to test for $AChPC_{20}$ is not always available in hospitals and clinics. It would therefore be worthwhile in future studies to examine the use of simpler tools, such as peak expiratory flow or questionnaires, that are widely used in general practice.

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