

An Early Intensive Intervention for Inducing Inactive Asthma in Adults—A One-Year Follow-Up Observation Study—

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ABSTRACT

Background: Treatment strategy that reduces dependence on long-term medication for chronic asthma is preferable. The purpose of the study is to investigate the efficacy of an early intensive intervention for inducing inactive asthma in adults and identify factors that affect the efficacy.

Methods: A prospective study was conducted on subjects who had asthma for two years or less. An intensive intervention consisting of systemic corticosteroid treatment for two weeks followed by inhaled corticosteroid for further 16 weeks with concomitant administration of bronchodilator(s) was administered on 109 subjects. As a control group, 33 subjects were treated according to the current asthma treatment guidelines for 18 weeks. The primary outcome of the intervention was assessed with symptomatology and use of medication during 12 months after the cessation of treatment period.

Results: At one year after the intervention, significantly more patients in the intensive intervention group (41%) than in the control group (24%) had no respiratory symptoms and were medication-free or had experienced minor upper respiratory symptoms (inactive asthma) ($P = 0.01$). The intensive intervention maintained a significant factor associated with one-year inactive asthma (adjusted odds ratio: 3.61, 95% confidence interval: 1.20–10.84; $P = 0.02$). Infection as onset cause, asthma duration and pre-treatment %FEV_{1.0} were also identified independently associated with inactive asthma. As the limitation, the study was not randomized trial.

Conclusions: Intensive therapy in the early stage is very likely to contribute to increasing one-year asthma inactivity, which may reduce patients' dependence on long-term management by medical treatment.

KEY WORDS

adult asthma, asthma therapy, corticosteroid, early intervention, inactive asthma

INTRODUCTION

Asthma patients who are faced with the prospect of long-term treatment expect to have effective treatments which could make asthma transient. Approximately 10% of adult asthmatics outgrow their asthma over long-term observation.¹ Early intervention using high-doses of inhaled corticosteroid (ICS) has shown a good prognosis for asthma.^{2,3} However, despite the

recent progress in asthma treatment, a definitive strategy for inducing long-term inactive asthma has not yet been reported. In this study, inactive asthma is defined as symptom-free condition that does not require any medication for one year.

To address the issue of inducing inactive asthma, we adopted the strategy that all asthmatics, regardless of onset mode, severity, and type of asthma in the early stage, should be treated with a view to in-

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Received 14 October 2010. Accepted for publication 16 January 2011.
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ducing inactive asthma using intensive treatment for a longer period than usually prescribed, coupled with early diagnosis of asthma and patient education. In contrast to the current guidelines for asthma treatment,^{4,6} which focus on establishing control of asthma with medication, our approach uses the step-down method from intensive treatment through tapering and finally cessation of treatment regardless of disease severity at the time of presentation. Our strategy is driven by the hypotheses that airway inflammation may not be necessarily chronic at the onset of asthma and that intensive strategic therapy with systemic corticosteroids may be more effective for achieving long-term inactive asthma if it is introduced in the early stages of asthma. The present study is not the comparison with International Asthma Guidelines for long-term management as the treatment strategy.

We conducted a one-year follow-up study of an intensive therapy for the early stage of asthma in adults as a trial for assessing how to prolong the remission period after cessation of intensive asthma treatment.

The objectives of the study were to evaluate the effectiveness of the early intensive intervention for adult asthma in inducing inactivity in asthma over a one-year period and identify factors that increased the one-year inactivity rate.

METHODS

SUBJECTS

Patients who visited the outpatient department or were admitted to the hospital during the period from May 1997 to January 1999 and had asthma for less than 2 years in duration were screened for enrollment ($n = 195$). Both newly-diagnosed asthmatics and previously-diagnosed asthmatics were included.

Patients who gave informed consent to undergo the proposed treatment received the intensive protocol therapy ($n = 112$, median age, 44, [range, 17-73]). Patients, who did not, received the standard therapy as recommended in the guidelines ($n = 35$, median age 42, [range, 19-73]).⁷⁻⁹

The protocol of this research was approved by the ethics review board of the National Center for Global Health and Medicine (NCGM). Verbal informed consents from all patients were taken using the study explanation note and recorded on the patients' charts by performed researchers. There was no obligation of written informed consent at the time of study performance and this process was approved by the ethical review board in NCGM (Ethical committee approval No. 127).

DIAGNOSTIC CRITERIA FOR ASTHMA FOR STUDY ENROLLMENT

In accordance with the diagnostic criteria in the GINA guidelines,⁸ patients were diagnosed with asthma if they showed a 15% or greater within- and

between-day variation in peak expiratory flow (PEF) and a 15% or greater improvement in PEF in response to bronchodilator(s).

Bronchial hyperresponsiveness (BHR) was measured by methacholine provocation testing in each participant, except those with unstable or severe asthma at presentation. Positive BHR was defined as provocation concentration of methacholine causing a 20% decrease in base-line of FEV_{1.0} (PC₂₀) < 8.0 mg/mL.^{10,11}

Subjects whose asthma onset was considered insidious had airway symptoms such as cough, or sputum or dyspnea for over one month and met the above mentioned criteria for air-flow limitation as well as positive BHR.

EXCLUSION CRITERIA FOR STUDY ENROLLMENT

Subjects were not eligible for enrollment if they had any of the following diseases or conditions:

1. Post infectious bronchitis (acute bronchitis), bronchiolitis, chronic bronchitis, pulmonary emphysema or endo-bronchial tuberculosis.

Post-infectious bronchitis was diagnosed based on its response to pharmacotherapy, which occasionally included antibiotics for airway infection, with disappearance of symptoms within one month of enrollment. Pulmonary emphysema was diagnosed by chest high-resolution computed tomography (HRCT)¹² and decreased diffusion capacity on pulmonary function tests (less than 80% of the predicted values). Bronchiolitis was diagnosed by characteristic chest HRCT findings.¹² Asthma patients who had symptoms similar to those of cough variant asthma^{13,14}, but met the above mentioned diagnostic criteria were enrolled. Gastroesophageal reflux disorder (GERD)^{15,16} was diagnosed based on the effectiveness of proton pump inhibitor (PPI) or H₂-blockers, and little reversibility of PEF. However, patients who had asthma complicated by GERD were enrolled.

2. Current heavy smokers with a smoking index of 400 or more. Smoking index was defined as the number of cigarettes per day multiplied by the number of smoking years.

3. Occupational and drug-induced asthma for which the etiological agent was known.

4. Recurrence of adult asthma from childhood asthma with a inactive duration of less than 3 years.

5. Allergic bronchopulmonary *Aspergillosis* or mycosis, Churg-Strauss syndrome and pulmonary infiltration with eosinophils.

6. Subjects who concurrently suffered from diabetes mellitus, or were at risk of becoming steroid-induced diabetics, for example, those with obesity, or a familial predisposition.

7. Subjects who were pregnant or wished to become pregnant during the study period.

ASTHMA ONSET MODE

Acute type was defined by dyspnea or severe cough that occurred suddenly with an identifiable onset. Chronic type was defined by airway symptoms, such as cough, sputum or dyspnea that started insidiously without an identifiable onset, but with a presumable approximate duration.

INTENSIVE TREATMENT PROTOCOL

After an initial 1-2 week observation period for clinical examinations, non-emergency patients who had agreed to the intensive protocol were given oral corticosteroids (prednisolone, 0.5 mg or equivalent/kg/day) for 2 weeks. A basic unit dose of prednisolone was presumed to be 5 mg. Doses 2.5 mg or less were scored as zero, and doses larger than 2.5 mg were scored as 5 mg. Intravenous administration of hydrocortisone at a dose of 300 mg every 8 hours was started in emergency cases and continued until the patient's condition improved and oral corticosteroid administration became possible. Systemic administration of corticosteroids for 2 weeks was then switched to inhaled beclomethasone dipropionate (BDP) at a dose of 800 µg/day for the next 8 weeks and then 400 µg/day for the remaining 8 weeks with the aid of a spacer. Other anti-asthma drugs, including bronchodilators or leukotriene receptor antagonists, were administered during initiation of the therapy and antibiotics were given when a patient was found to have a bacterial airway infection based on clinical judgment and sputum culture. With the exception of the inhaled corticosteroids, these drugs were stopped during the course of treatment when the patients' PEF reached normal levels or symptoms of infection disappeared. The conventional therapy including inhaled corticosteroid, which was given to patients not wishing to receive the intensive therapy, was administered in accordance with the guidelines for asthma severity.⁷⁻⁹ For patient education, all participating patients received verbal instructions and pamphlets concerning the elimination and avoidance of environmental risk factors and improving compliance with medication.

TREATMENT PROTOCOL FOR RECURRENCE OR WORSENING OF ASTHMA

In cases of non-acute exacerbation, recurrence or worsening of asthma was defined as a greater than 10% decrease in PEF from the baseline value with respiratory symptoms of more than one week in duration. When these conditions were observed during the treatment or follow-up period, the patient was treated with 800 µg/day of inhaled BDP for 2 weeks followed by 400 µg/day for the next 2 weeks as well as appropriate bronchodilators. Acute exacerbations were treated with systemic corticosteroids with bronchodilators for appropriate duration. After recovery,

the basal therapy was resumed.

PREVENTION OF SIDE EFFECTS OF SYSTEMIC CORTICOSTEROIDS

During the first 2 weeks of treatment, patients were simultaneously given a H₂-blocker prophylactically. Anti-hypertensive agents were also administered when required and appropriate hypnotics were administered when sleep disturbance manifested. After 2 weeks of systemic administration, patients were requested to avoid physical stress for 1 week to allow for recovery from adrenal suppression.¹⁷

STUDIES DURING THE TREATMENT COURSE AND FOLLOW UP AFTER TREATMENT

Pulmonary function tests, bronchial provocation testing, serum IgE, specific IgE antibodies, and the peripheral eosinophil blood count were examined before treatment and at 0, 6, and 12 months after treatment. Daily PEF was recorded during the study. At the end of the study, patients were face-to-face interviewed or telephone interviewed using a structured questionnaire and a questionnaire was sent by mail to those who had stopped visiting the outpatient clinic.

CATEGORIZATION OF OUTCOME OVER 12 MONTHS

The outcome over the one-year period after the tentative cessation of any pharmacotherapy was categorized into 3 groups (inactive, intermittent, and chronic) according to 6 conditions on the basis of clinical profiles.

Inactive

Condition 1: no respiratory symptoms and medication-free.

Condition 2: upper respiratory tract infections, such as a common cold or short term respiratory symptoms with a known trigger, but not requiring anti-asthma drugs because symptoms and PEF recovered within one week.

Intermittent

Condition 3: asthma transiently worsened for one week or more, but the condition normalized following a course of the rescue protocol.

Chronic

Condition 4: the rescue protocols were given twice or more, or asthma symptoms reappeared after cessation of treatment.

Condition 5: asthma control required basic maintenance therapy even after completion of pharmacotherapy.

Condition 6: asthma symptoms reappeared after the patients elected to discontinue pharmacotherapy and their decision to resume treatment or not was made based on the mildness of the disease. Condi-

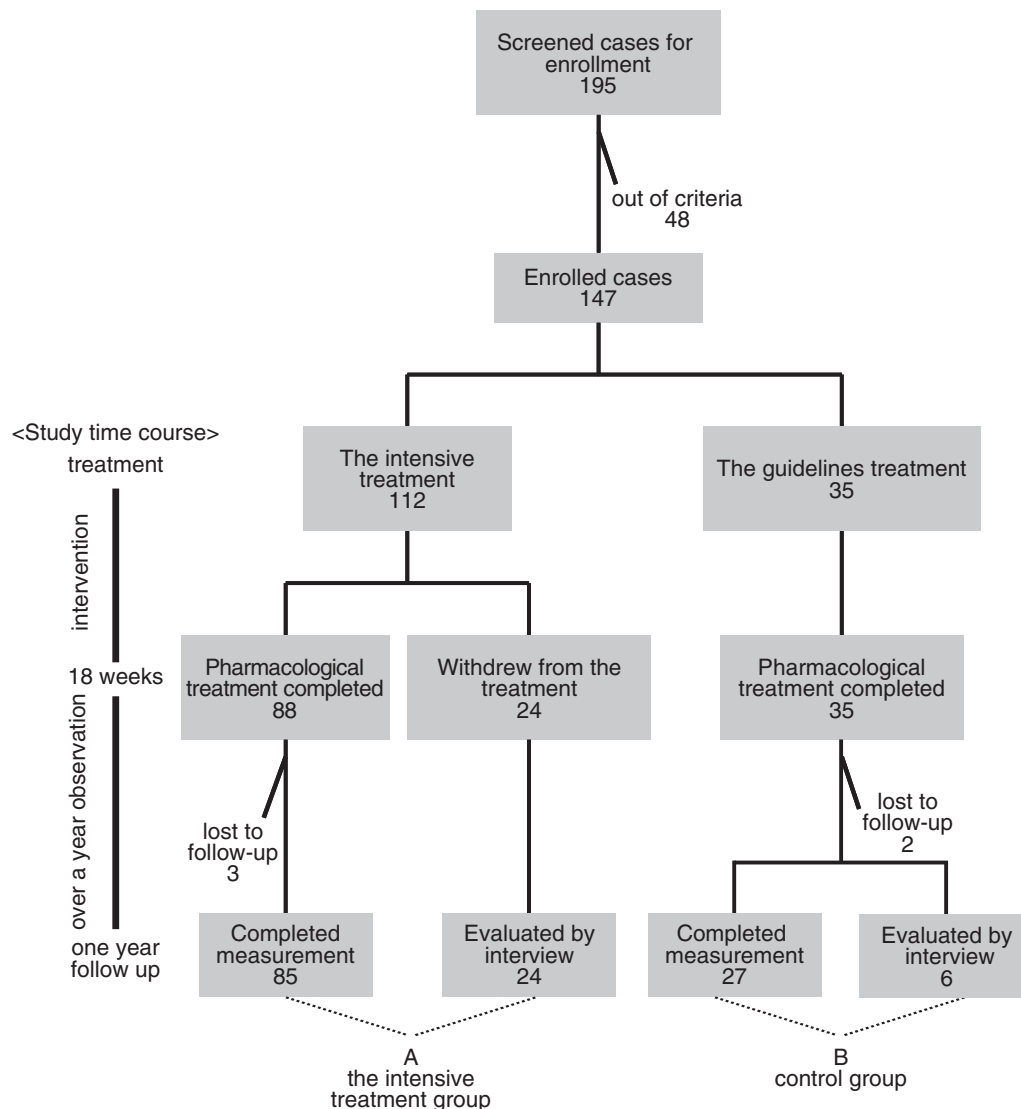


Fig. 1 Study population. 195 cases were screened for enrollment. 147 cases were enrolled to the study. Finally 109 (85/24) cases for the intensive treatment group, 33 (27/6) cases for the guideline treatment group were evaluated for the one year outcome of prognosis. 24 cases in intensive treatment group, 6 cases in the guideline treatment group respectively, evaluated by face-to-face or telephone interview using the structured questionnaire.

tion 6 was identified by interview using questionnaire at the end of the one-year follow-up period.

STATISTICAL ANALYSIS

Patient characteristics were compared between the intervention and control groups using unpaired t-test, Pearson's chi-square test, or Fisher's exact test. The one-year outcome for the two groups was compared using the Mann-Whitney test. A univariate logistic regression analysis was used to identify variables that were significantly associated with the inactive asthma outcome. A multivariate logistic regression analysis was conducted to determine the effects of each pa-

tient characteristic on the efficacy of the intensive intervention. The forward stepwise procedure was used to develop a final model for predicting outcomes. The fitness of the final model was investigated using the Hosmer-Lemeshow test and by calculating receiver operator characteristic (ROC) curves. The course of PC₂₀ from pre-treatment to 18 weeks after the end of regimen and 12 months thereafter was recorded, and the difference between two groups was compared using a mixed model. All P values are two-tailed with a P value < 0.05 considered statistically significant. Data analyses were conducted using PASW statistical software (version 17; SPSS Inc. Chicago, IL, USA).

Table 1 Pre-treatment patient characteristics

	Intensive treatment group <i>n</i> = 109	Control group <i>n</i> = 33	<i>P</i> value*
Age — yr			0.55
Median	44	42	
Range	17-73	19-73	
Male sex — no.(%)	56 (51)	20 (61)	0.35
Allergic or asthma condition — no. (%)			
Type of asthma — atopic	74 (68)	23 (70)	0.90
Other allergic diseases †	49 (45)	14 (42)	0.80
Complicating diseases ‡	69 (63)	15 (45)	0.07
Smoking			0.70
non smoker	41 (38)	15 (45)	
ex-smoker	4 (5)	2 (6)	
passive smoker	18 (17)	6 (18)	
active current smoker	45 (41)	10 (58)	
Indoor pet	43 (39)	9 (27)	0.20
Allergic disease in family	35 (32)	15 (45)	0.16
Asthma onset mode			0.25
chronic	71 (65)	25 (76)	
acute	38 (35)	8 (24)	
Infection as onset cause §	71 (65)	20 (61)	0.64
Asthma duration —month ± SD**	7.9 ± 7.8	8.1 ± 8.0	0.91
Condition at presentation			0.03
chronic	73 (67)	29 (88)	
acute	35 (32)	4 (12)	
Severity ¶			0.29
Severity I	11 (10)	6/33 (18)	
Severity II	58 (53)	19/33 (58)	
Severity III	35 (32)	7/33 (21)	
Severity IV	4 (4)	0	
Laboratory findings			
Log IgE***	5.5 ± 1.4	5.5 ± 1.3	0.87
Log Eos****	5.9 ± 0.9	5.8 ± 0.8	0.75
%FVC#, *****	96.2 ± 15.3	100.0 ± 17.8	0.26
%FEV _{1.0} #	87.6 ± 19.6	91.7 ± 17.3	0.27
%PEF _{min} ††	69.9 ± 19.1	72.2 ± 15.4	0.65
Log PC ₂₀ #	6.0 ± 1.6	6.1 ± 1.2	0.71

**P* value were tested using Chi-square test or Fishers exact test.

Abbreviations: **SD, standard deviation; ***IgE, total IgE antibody in serum; ****Eos, count of peripheral eosinophil; *****FVC, forced vital capacity of volume.

† Allergic rhinitis, sinusitis, conjunctivitis, dermatitis.

‡ Alcohol induced asthma, exercise induced asthma, gastro-esophageal reflux disorder.

§ Most infection episodes are viral infections diagnosed by symptomatology and clinical data. Three cases were post mycoplasma pneumonia infection.

¶ Severity of the asthmatic condition was judged according to the classification of long term severity for chronic state or of acute exacerbation for acute state in EPR II.⁷

Severe or unstable cases are excluded that could not endure BHR and pulmonary function tests.

†† Minimum PEF was the minimum value of PEF during the observational period. %value of PEF is calculated by the standard values established by the study of the normal Japanese population.²³

Table 2 One year prognosis

Category		No. (%) of the intensive treatment group <i>n</i> = 109	No. (%) of the control group <i>n</i> = 33
Inactive	Condition 1	36 (33)	4 (12)
	Condition 2	9 (8)	4 (12)
	Total of conditions on 1, 2	45 (41)	8 (24)
Intermittent	Condition 3	15 (14)	0 (0)
Chronic	Condition 4	22 (20)	12 (36)
	Condition 5	11 (10)	3 (9)
	Condition 6	16 (15)	10 (30)
	Total of conditions on 4, 5, 6	45 (45)	25 (75.8)

Mann-Whitney test; $P = 0.01$.

Prognosis during the one year after the cessation of any pharmacotherapy was categorized into six conditions.

Condition 1: no respiratory symptoms and medication-free.

Condition 2: upper respiratory tract infections symptoms but not requiring anti-asthma drugs.

Condition 3: asthma transiently worsened for one week or more, but normalized following a course of the rescue protocol.

Condition 4: the rescue protocols were given twice or more, or asthma symptoms reappeared after cessation of treatment.

Condition 5: asthma control required basic maintenance therapy after completion of medication.

Condition 6: asthma symptoms reappeared after the patients elected to discontinue medication.

RESULTS

STUDY POPULATION

Of the 195 subjects who were screened for enrollment, 147 were eligible for the study. After excluding the data of 5 subjects who dropped out of the study, 142 subjects (109 subjects comprised the intensive treatment group, $n = 109$; control group, $n = 33$) were enrolled for analysis (Fig. 1).

PATIENT CHARACTERISTICS

No significant difference in demographic and baseline clinical characteristics were observed between the intensive treatment and control groups, except in terms of whether asthma condition at presentation was acute or chronic ($P = 0.03$) (Table 1).

ONE-YEAR OUTCOME

The outcome during the one-year period following the pharmacological therapy is shown in Table 2. Inactive asthma at one year after treatment was achieved for 41% and 24% of the patients in the intensive treatment group and the control group, respectively. However, 45% and 76% of patients in the intensive treatment group and the control group, respectively, still had chronic asthma. The prognosis of the intensive treatment group was significantly better than the guidelines treatment group ($P = 0.01$). No serious side effects occurred on the patients under the treatment of systemic corticosteroid for two weeks with preventive medical care.

PATIENT CHARACTERISTICS ASSOCIATED WITH INACTIVE ASTHMA AT ONE YEAR AFTER TREATMENT

Patients' pre-treatment characteristics, including both treatment regimens in this study, were investigated for association with inactive asthma at one year after treatment (Table 3). Clinical background and laboratory data (history of allergy, obstructive pulmonary disease, and BHR) were selected in consideration of the pathophysiology of asthma. Intensive treatment had an odds ratio of 2.20 (95% CI, 0.91-5.31) for inactive asthma at one year after treatment. Some histories of illness, such as asthma onset mode, infection as onset cause, and condition at presentation, were also associated with outcome. Asthma duration emerged as a significant factor affecting inactive asthma at one year after treatment, with longer durations being less likely to result in inactive asthma ($P < 0.01$). Asthma severity tended to be associated with inactive asthma, although this association was not statistically significant ($P = 0.06$). Results of pulmonary function tests, such as %FVC and %FEV_{1.0}, %PEF_{min} and Log PC₂₀, at the beginning of the treatment were significantly associated with inactive asthma at one year after treatment in patients who first presented with a mild or stable condition that allowed them to complete these tests. Thus, in patients with a mild or stable condition, better pulmonary functions and less BHR were indicators of a good prognosis (Table 3).

THE EFFECT OF INTERVENTION AFTER ADJUSTMENT

A multivariate logistic regression analysis was conducted to determine the influence of possible confounding factors among patient characteristics in con-

Table 3 Pre-treatment characteristics and their odds ratio for inactive asthma

Factor	Odds ratio (95% confident interval)		P value
Intensive intervention	2.20	(0.91-5.31)	0.008
Age - yr	1.00	(0.98-1.02)	0.72
Male sex	0.85	(0.43-1.68)	0.64
Type of asthma type (atopic /non-atopic)	0.82	(0.39-1.69)	0.58
Other allergic diseases [†]	0.94	(0.47-1.86)	0.86
Complicating diseases [‡]	0.96	(0.48-1.91)	0.90
Smoking	1.05	(0.82-1.35)	0.71
Indoor pet	1.23	(0.61-2.48)	0.57
Allergic disease in family	1.05	(0.51-2.13)	0.90
Asthma onset mode (acute/chronic)	0.34	(0.15-0.77)	0.01
Infection as onset cause [§]	2.67	(1.24-5.74)	0.01
Condition at presentation (acute/chronic)	2.55	(1.20-5.43)	0.02
Asthma duration - month	0.81	(0.74-0.89)	<0.01
Severity [¶] I	2.67	(0.23-31.07)	
Severity II	2.50	(0.25-25.12)	
Severity III	0.82	(0.08-8.84)	
Severity IV	1		0.06
Log IgE [*]	0.93	(0.73-1.20)	0.59
Log Eos ^{**}	0.86	(0.58-1.28)	0.45
%FVC ^{***}	1.03	(1.01-1.06)	0.01
%FEV _{1.0} [#]	1.04	(1.02-1.07)	<0.01
%PEF _{min} ^{††}	1.03	(1.01-1.06)	0.01
Log PC ₂₀ [#]	2.02	(1.46-2.79)	<0.01

Abbreviations: *IgE, total IgE antibody in serum; **Eos, count of peripheral eosinophil; ***FVC, forced vital capacity of volume.

[†] Allergic rhinitis, sinusitis, conjunctivitis, dermatitis.

[‡] Alcohol induced asthma, exercise induced asthma, gastro-esophageal reflux disorder.

[§] Most infection episodes are viral infections diagnosed by symptomatology and clinical data. Three cases were post mycoplasma pneumonia infection.

[¶] Severity of the asthmatic condition was judged according to the classification of long term severity for chronic state or of acute exacerbation for acute state in EPR II.⁷

[#] Severe or unstable cases are excluded that could not endure BHR and pulmonary function tests.

^{††} Minimum PEF was the minimum value of PEF during the observational period. %value of PEF is calculated by the standard values established by the study of the normal Japanese population.²³

Table 4 Adjusted odds ratio of intensive intervention and other pre-treatment characteristics for inactive asthma

Factor	Odds ratio (95% confident interval)		P value
Intensive intervention	3.61	(1.20-10.84)	0.02
Infection as onset cause [†]	2.99	(1.13-7.93)	0.03
Asthma duration (month)	0.85	(0.77-0.93)	<0.01
%FEV _{1.0} [‡]	1.04	(1.01-1.07)	<0.01

[†] Most infection episodes are viral infection diagnosed by symptomatology and clinical data. Three cases were post mycoplasma pneumonia infection.

[‡] Severe or unstable cases were excluded that were unable to endure pulmonary function tests.

sideration of the effect of the intensive treatment (Table 4). After adjusting for possible confounding factors, the intensive intervention maintained a high odds ratio of 3.61 (95% CI, 1.20-10.84; $p = 0.02$) for inactive asthma at one year after treatment. Infection as onset cause, asthma duration and %FEV_{1.0} were also independently associated with inactive asthma. The Hosmer-Lemeshow test of the final model had a p value of 0.55 and the area under the ROC curve for the model was 0.86 (95% CI, 0.79-0.92), indicating that the model had good fitness.

BHR COURSE

The course of BHR was also compared between the intensive intervention group and control groups (Fig. 2). The BHR of patients in the intensive treatment group showed higher improvement at 18 weeks after the treatment than the one of control group. The ef-

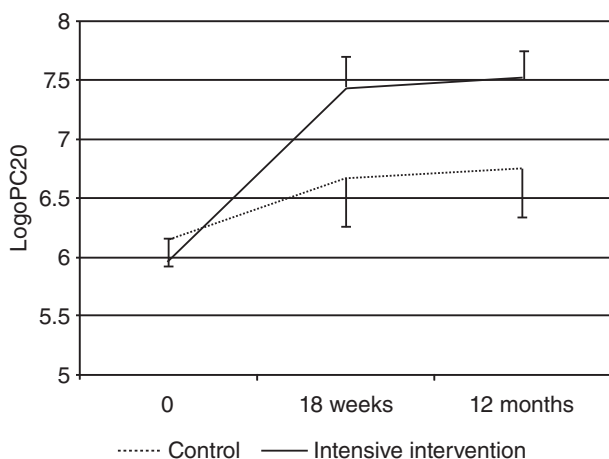


Fig. 2 Bronchial hyperresponsiveness course. The mean of PC₂₀ of each group was indicated with vertical bars of the estimated standard errors. The course of BHR was compared between the intensive intervention group and the control treatment group. The effect of intensive intervention was statistically significant ($p = 0.01$ as an interaction of treatment and time).

fect of intensive intervention was statistically significant ($p = 0.01$ as an interaction of treatment and time). By the end of the one-year follow-up, the mean value of PC₂₀ in the intensive treatment group had been maintained.

DISCUSSION

Approximately 10% of adult patients with asthma have been reported to outgrow their asthma with treatment.¹ The current guidelines for asthma treatment focus on establishing control of asthma with medication; therefore, improving our understanding of the patient characteristics that indicate the potential for remission, may allow us to induce inactive asthma in a larger percentage of patients.

Previous early intervention therapy with high-dose inhaled corticosteroid was unable to induce long-term disease inactivity, although several cases of inactive asthma have been reported.² This may be because the potency of even high-dose inhaled corticosteroid alone might not have been sufficient for inducing inactive asthma.¹⁸

The treatment protocol used in this study was designed around an intensive drug regimen, namely systemic corticosteroid administration for 2 weeks switched to local corticosteroid administration for 16 weeks, to encompass treatment for all situations of asthma onset. The 18-week duration of treatment adopted in the study is comparable to the protocols used for other respiratory diseases, in which most cases are sent into remission, for instance; Bronchiolitis Obliterans Organizing Pneumonia¹⁹/Cryptogenic Organising Pneumonitis and Acute Eosino-

philic Pneumonia.^{20,21} The treatment was carried out to avoid the adverse reactions associated with short-term systemic administration. During the study period, no serious side effects occurred under these study conditions. Systemic corticosteroid administration for 2 weeks alone was not enough to achieve one-year inactivity of asthma, as was demonstrated by the cases that dropped out during the treatment course.

The present study identified the following four significant factors that were associated with inactivity of asthma at one year after treatment: intensive therapy, infection as onset cause, asthma duration, and %FEV_{1.0} (Table 4). Among these factors, early diagnosis and the intensity of the treatment are amenable to physicians.

Overall, the intensive intervention used in this study showed high efficacy. At one year after treatment, 32 of 43 (74%) subjects who completed the intensive treatment and whose asthma duration was 6 months or less had inactive asthma. Furthermore, 26 of 32 (81%) subjects who completed the intensive treatment and whose asthma duration was 3 months or less had inactive asthma at one year after treatment. This strongly suggests that the early introduction of intensive treatment coupled with early diagnosis has a considerable impact on asthma prognosis.

Although the results of a multivariate logistic regression analysis indicated that infection as onset cause was also a good indicator for a favorable outcome, it remains unclear why this factor was important.

In addition, %FEV_{1.0} was identified as an indicator of good prognosis. Although data are only available from patients who could complete the pulmonary function tests at the time of presentation, even most cases with severe and acute onset asthma at presentation had inactive asthma at one year after the early intensive intervention. A previous report speculated that %FEV_{1.0} is associated with prognosis¹; thus, the present findings seem to confirm the presence of an association.

There are limitations to this study. First, this study was not a randomized trial. Therefore, other possible confounding factors could have affected the outcome, even after adjustment. Second, this research was a small-scale, single-center study. Consequently, the number of subjects was not large enough to allow for generalization. Third, as no gold standard diagnostic criteria have been established for asthma, some patients in this study may not have developed chronic asthma in the future. Although the new methods to measure airway inflammations such as fraction of exhaled nitric oxide have been currently developed,²² no use those aspects for this study. In spite of these limitations, the present findings suggest that the early intensive intervention could induce inactive asthma for one year.

The treatment strategy for adult asthma in early

stage was proposed in the study. This strategy requires early diagnosis and adequate treatment intensity, and appears to be applicable regardless of asthma severity at presentation. Our findings suggest that early intensive intervention is effective for inducing inactive asthma in adults. It assists to develop certain treatment strategies which can increase a rate of outgrow in adult asthma with further large-scale, randomized trials.

ACKNOWLEDGEMENTS

The authors thank to Dr. James G Martin, Professor, Department of Medicine, McGill University, Canada, for his helpful comments on the manuscripts.

A research grant was supported by the Ministry of Health, Labour and Welfare for the program No. H18-Immunology and Allergy-005.

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