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ORIGINAL ARTICLE

# A Study of the Usefulness of Anti-inflammatory Treatment for Mild Intermittent Asthma (Step 1): Budesonide vs. Montelukast

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## ABSTRACT

**Background:** Early intervention in adult asthma has been evaluated mostly with regard to symptoms, respiratory function and airway hyperresponsiveness, and has rarely been evaluated with regard to airway inflammation. Further, no clinical data concerning prevention of remodeling by anti-inflammatory therapy have been reported. The anti-inflammatory activities of an inhaled steroid and a leukotriene receptor antagonist were compared using sputum induced by inhaled hyperosmotic NaCl solution, and the usefulness of anti-inflammatory treatment for mild intermittent asthma (step 1) was investigated.

**Methods:** The subjects of the study were patients with mild intermittent asthma (step 1) who had not received steroid treatment and had only been treated with inhaled β2-stimulants as needed. The subjects were divided into two groups : one group received 400 μg/day of budesonide (BUD group ; $n$ = 15) and the other group received 10 mg/day of montelukast (MK group ; $n$ = 12). The anti-inflammatory activities of BUD and MK were compared by examining respiratory function, exhaled nitric oxide (ENO) concentrations, airway hyperresponsiveness (acetylcholine provocation test) and the sputum induced by inhalation of hyperosmotic NaCl solution at three time points, *i.e.*, before, 1 month after, and 6 months after the start of treatment.

**Results:** It was shown that even in mild intermittent asthma (step 1) the levels of ENO and sputum eosinophil ratio were elevated, indicating that airway inflammation was clearly present and that airway hyperresponsiveness was elevated. The effects of BUD and MK in improving ENO and sputum eosinophil ratio were almost the same. However, airway hyperresponsiveness in both groups were not significantly improved after 1 and 6 months of treatment.

**Conclusions:** Anti-inflammatory treatment is necessary even for mild intermittent asthma (step 1). We believe that early intervention with anti-inflammatory drugs is important for the prevention of airway remodeling, exacerbation of disease and progression to intractable asthma. Either of the two types of drugs, low-dose inhaled steroids or leukotriene receptor antagonists, can be selected as anti-inflammatory drugs for mild intermittent asthma.

## KEY WORDS

airway hyperresponsiveness, airway inflammation, anti-inflammatory treatment, early intervention, exhaled nitric oxide, induced sputum, mild intermittent asthma

## *INTRODUCTION*

Bronchial asthma is defined by three characteristics, *i.e.*, reversible airway constriction, enhancement of airway hyperresponsiveness and airway inflammation, of which the latter is considered an important factor in bronchial asthma.[1] The airway inflammation seen in bronchial asthma is chronic allergic inflam-

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**Table 1** Characteristics of the study subjects

| | BUD400 group | MK group | *p* value |
|---|---|---|---|
| N | 15 | 12 | |
| Male/Female | 10/5 | 5/7 | 0.1939 |
| Age, years | 36.2±12.8 | 35.6±14.4 | 0.9097 |
| Atopy/Non-atopy | 9/6 | 8/4 | 0.7215 |
| Duration of asthma (years) | 10.4±12.8 | 13.3±14.0 | 0.5796 |
| $FEV_{1.0}$/FVC ratio (%) | 79.1±10.4 | 83.6±8.7 | 0.2417 |
| $FEV_{1.0}$, as percent of the predicted value | 88.8±12.5 | 94.5±9.9 | 0.2096 |

mation characterized by injury of airway epithelia due to the infiltration of inflammatory cells consisting mainly of eosinophils. Allergy, infections with viruses etc. and various environmental factors are involved in the etiology of chronic inflammation. These acquired factors induce infiltration into airways and activation of inflammatory cells such as eosinophils, Th2 cells and neutrophils to release inflammatory mediators and cytokines. The interaction of these inflammatory mediators and cytokines then causes airway inflammation leading to injury of airway epithelia. It is believed that the injury of airway epithelia combined with constriction of airway smooth muscles leads to enhancement of airway hyperresponsiveness. In patients with bronchial asthma, which is a chronic disease, even during periods when there are no asthma attacks, the numbers of eosinophils in bronchoalveolar lavage fluid and sputum and the level of eosinophil cationic protein (ECP) are higher than in healthy subjects, indicating the presence of airway inflammation. The degree of airway inflammation and that of airway hyperresponsiveness correlate well, and airway inflammation is therefore considered the cause of airway hyperresponsiveness.[2-6]

In guideline (1) of GINA2002 (Global Initiative for Asthma 2002), it is noted that, for the treatment of chronic adult asthma of mild intermittent type (step 1), giving β2-stimulants alone only during periods of disease exacerbation is sufficient and that regular anti-inflammatory treatment using inhaled steroids etc. is not necessary. However, it has been reported that, even during periods when there are no asthma attacks in patients with mild intermittent asthma, airway inflammation exists.[7] Therefore, it is expected that, if anti-inflammatory therapy for mild intermittent asthma is not started early, exacerbation of airway inflammation will occur in some patients, leading to more frequent attacks of asthma, progression of airway remodeling and more severe and intractable asthma.

The subjects of the present study were patients with mild intermittent asthma who did not have asthma attacks at the time of the study and who had not received regular anti-inflammatory treatment such as inhaled steroids and had received only inhaled β2-stimulants as needed. The measurement of exhaled nitric oxide concentration, the airway hyperresponsiveness test and examination of sputum induced by inhalation of hyperosmotic NaCl solution were carried out before the treatment was started. Then, inhaled steroid and leukotriene receptor antagonist were prescribed. After 1 month and 6 months of treatment, similar tests were performed and the inhibitory effects of the two drugs on airway inflammation and airway hyperresponsiveness were compared and the usefulness of the anti-inflammatory treatment and early intervention for mild intermittent asthma were examined. This study was approved by the ethics committee of National Minami-Fukuoka Hospital and all the participants signed the patient informed consent forms.

## *METHODS*

### SUBJECTS

The subjects in this study were 27 outpatients with mild intermittent asthma who visited the Department of Allergy at National Minami-Fukuoka Hospital. None of them had received regular anti-inflammatory treatment such as inhaled steroids. They had been treated only with inhaled β2-stimulants as needed. The diagnosis and judgment of severity of asthma were performed according to the guidelines of GINA 2002. There were no asthma attacks in any of the patients at the time of clinical examination. The subjects were randomly divided into two groups : a budesonide 400 μg/day group (BUD group ; $n$ = 15) and montelukast 10 mg/day group (MK group ; $n$ = 12). There were more male patients in the BUD group and there were more female patients in the MK group. There were no significant differences in age, presence of atopy/ non-atopy or duration of asthma between the two groups, and respiratory function was normal in both groups. No significant differences in FEV1/FVC ratio and FEV1, as percent of the predicted value, were found between the two groups before treatment (Table 1).

### STUDY DESIGN

Before the treatment, measurement of exhaled nitric oxide concentration, measurement of flow-volume curves, the airway hyperresponsiveness test (acetylcholine provocation test) and examination of sputum induced by inhaled hyperosmotic NaCl solution were carried out in this order, and then treatment with 400 μg/day of budesonide or 10 mg/day of montelukast was started. After 1 month and 6 months of treatment, similar examinations were performed and the inhibitory effects of the two drugs on airway inflammation and airway hyperresponsiveness were compared.

Inhaled β2-stimulant was withheld for 48 hours

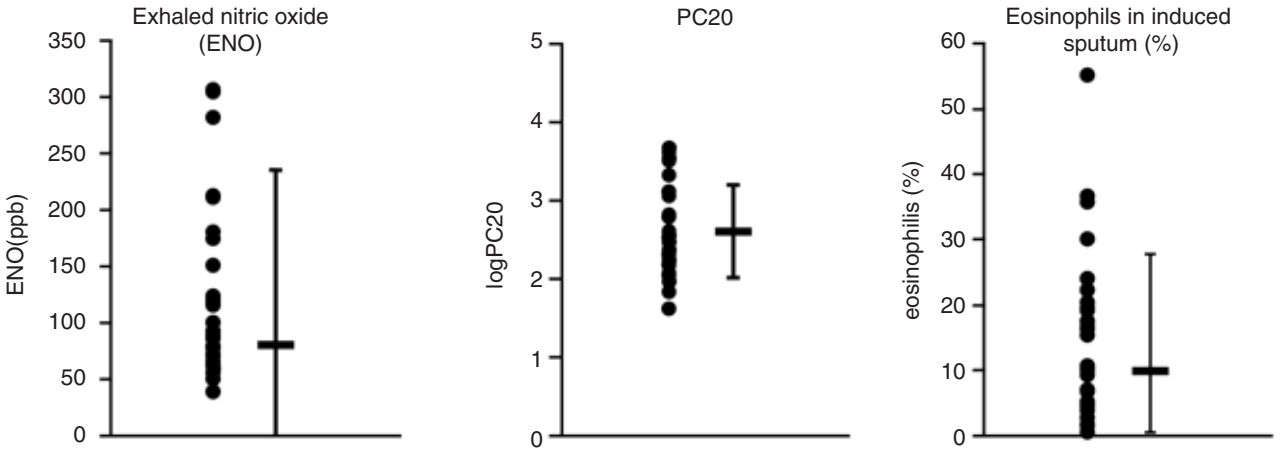


**Fig. 1** Exhaled nitric oxide (ENO) concentration, PC20 and sputum eosinophil ratio in mild intermittent asthma (step 1) (Pretreatment: $n = 27$). Even in cases of mild intermittent asthma, exhaled nitric oxide (ENO) concentration and sputum eosinophil ratio were elevated. Airway inflammation and elevated airway hyperresponsiveness were present. PC20 is expressed as logPC20.

prior to the clinical examinations, and no subjects received other asthma medications, including inhaled or oral steroid therapy.

After confirming that FEV1 was more than 80% of the predicted value,a blood sample was collected for the measurement of IgE- radioimmunosorbent test (RIST) and IgE-RAST. The provocative concentration of acetylcholine which produced a 20% fall in FEV1 (mg/ml) (PC20) was measured in each subject (see below). Sputum induction was performed 15 minutes after recovery from the acetylcholine challenge test. Acetylcholine challenge does not affect sputum results.[8]

## MEASUREMENT OF EXHALED NITRIC OXIDE (NO) CONCENTRATION

The concentrations of exhaled nitric oxide were measured according to the guidelines of the American Thoracic Society (ATS) by the single-breath method (on-line measurement) using a fast response (0.02 S) chemiluminescence analyzer (NOA 280 ; Sievers Instruments Inc., Boulder, CO, USA).[9] While seated, the subjects breathed through a mouthpiece attached to a one-way valve. The valve had two sampling ports near the mouthpiece. NO was sampled directly into the analyzer through a Teflon side-arm tube attached to one of the sampling ports. The exhalation pressure was measured by a pressure transducer in the analyzer via the second sampling port. All measurements were made using a mouth pressure of 16 $cmH_2O$ corresponding to an expiratory flow of 75 ml/s. After inhalation to TLC, the subjects immediately exhaled into the mouthpiece. The mouth pressure was then displayed on a computer screen as a prompt for the subjects to maintain a steady flow. NO values were recorded as a plateau at the last part of the exhalation. Repeated exhalations were performed to achieve three NO values that agreed at the 5% level. NO concentrations were recorded as the average of these three values. Values of 20 parts per billion (ppb) and above were judged to be abnormal.

## MEASUREMENT OF FLOW-VOLUME CURVES

Forced vital capacity, FEV1, maximal expiratory flow at 50% and at 25% were measured with a spirometer (Superspiro, DISCOM-21FX, Chest M.I. Co., Tokyo, Japan). Results were expressed as percentage of predicted, based on relevant reference standards.[10]

## MEASUREMENT OF SERUM IgE-RIST AND IgE-RAST

Venous blood was obtained and serum IgE-RIST was measured using fluoroenzyme immunoassay (FEIA) (CAP RIST FEIA, Pharmacia, Uppsala, Sweden). Serum IgE-RAST was measured using FEIA (CAP RAST FEIA, Pharmacia).

## MEASUREMENT OF AIRWAY HYPERRESPONSIVENESS TO ACETYLCHOLINE

The challenge test was performed using the method of Makino *et al.*[11] All antiasthma medications were withheld for at least 48 hrs before measurement of airway hyperresponsiveness. Subjects inhaled acetylcholine aerosol from a hand-held nebulizer (Clinical air pump, model REB 30REPC-Medicare 24, Medicare Co., Yokohama, Japan) by tidal breathing for 2 min. The operating airflow rate was 5 l/min. The isotonic saline was inhaled first as a control. This was followed by doubling concentrations of acetylcholine from 0.039 to 20 mg/ml. The FEV1 was measured after each inhalation with a spirometer (Superspiro, DISCOM-21FX, Chest M.I. Co., Tokyo, Japan). The percentage FEV1 fall was calculated from the post saline-FEV1. The test was continued until the FEV1

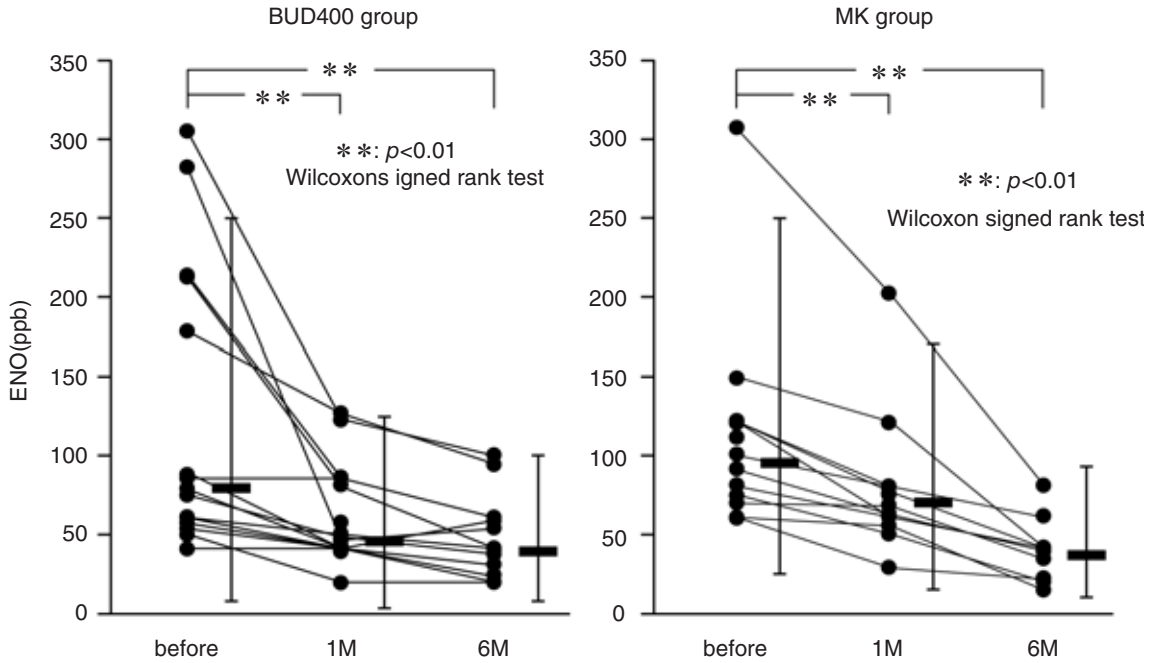


**Fig. 2** The time course of exhaled nitric oxide concentrations in the BUD and MK groups. The exhaled nitric oxide concentrations of the BUD group ($n$ = 15) were significantly lowered after 1 and 6 months of treatment compared to pretreatment level, but did not return to normal level. The MK group ($n$ = 12) had similar results. *$P$ < 0.05

had fallen > 20% or until the maximal concentration of acetylcholine had been administered. The airway hyperresponsiveness was expressed as PC 20. At the end of the test, any fall in FEV1 was reversed with an inhalation of salbutamol (0.3 ml of Venetlin® for inhalation). Subjects with PC20 of less than 8 mg/ml were considered to have airway hyperresponsiveness according to the criteria of the American Thoracic Society.[10]

## SPUTUM INDUCTION AND PROCESSING

### Sputum Induction

Sputum was induced by inhalation of 5 ml of 3% NaCl solution, using a small ultrasonic nebulizer ((NE-U12, OMRON Co., Tokyo, Japan). The output is about 5 L/min and the mean aerodynamic mass median diameters of the nebulized saline solution range from 1 to 5 μm, according to the manufacturer. Before coughing up sputum, subjects were asked to rinse their mouths, swallow saliva and water, and blow their noses, to minimize contamination with saliva and post-nasal drip. Subjects were asked cough during and after inhalation, and to expectorate into empty containers. Induction was discontinued once an adequate sputum sample had been obtained or 30 minutes had passed. Inhaled β2-stimulant (2 ml of saline and 0.3 ml of salbutamol solution with pressurized nebulizer) was premedicated. To check lung function, flow-volume curve measurements were made before and after sputum induction. If FEV 1.0 decreased by more than 10%, the subject was treated with additional inhalation of β2-stimulant. None of the subjects experienced marked adverse effects.

### Sputum Processing

Sputum was processed within 30 minutes. It was stored in a refrigerator at + 4℃ pending processing. Sputum samples were transferred to a Petri dish and the more viscous parts collected using forceps. Sputum plugs were first mixed with forceps. The samples were processed by a method described by Metso *et al.*[12] to collect cells for cytospin and cell-free supernatant. A four-fold volume of 6.5 mmol/L dithiothreitol (DTT) (SputolysinR, CalbioChem, LaJolla, California, USA ; diluted 10-fold in distilled water) was added to the sputum sample and the mixture was incubated for 15 minutes on a roller mixer at room temperature. An equal volume of phosphate-buffered saline (PBS, pH 7.2) was added, and incubation continued for another five minutes. The mixture was filtered through a 53 μm mesh nylon filter (Nybolt PA-53/35, Seidengaze, Germany). Sputum cells were separated by centrifugation at 2000 *g* for 10 minutes and the supernatant was collected for fluid-phase markers. Cells obtained after centrifugation were resuspended in 1 ml of PBS and the total number of cells was determined using a haemocytometer. Viability was measured by means of the trypan blue exclusion test (trypan blue stain 0.4%, GibcoBRL Life Tchnologies, UK). The cell suspension was cytocentrifuged (Cytospin 3, Shandon,

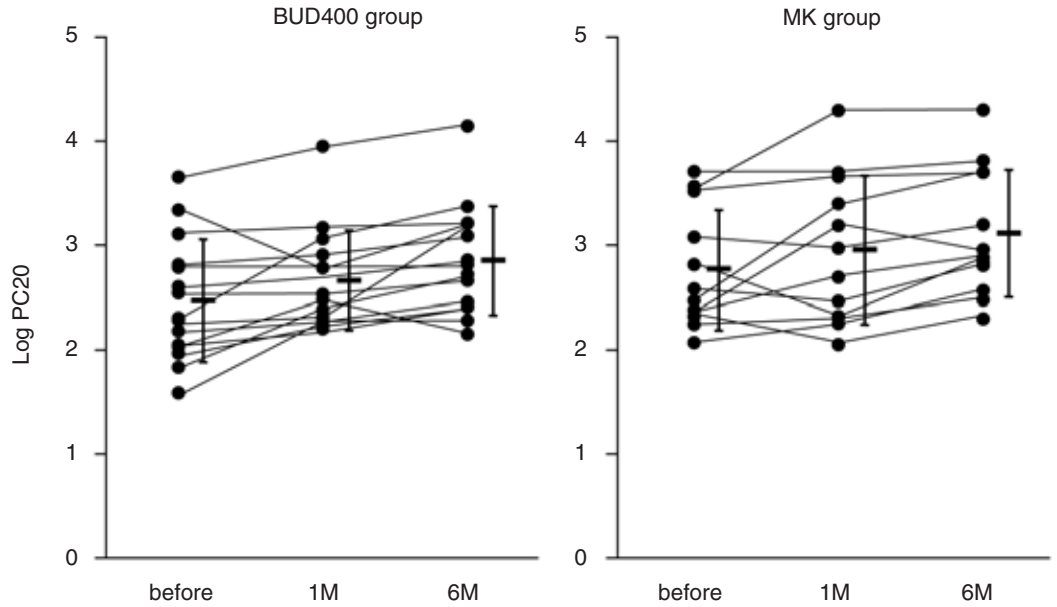


**Fig. 3** The time course of PC20 in the BUD and MK groups. The values of logPC20 in the both groups were not significantly improved after 1 and 6 months of treatment compared to pretreatment level.

Astmoor, UK) on to microscope slides (Super FrostR Plus, Menzel-Glaser, Germany) at 450 rpm for six minutes. Cytospins from sputum were allowed to dry in the air for 30 minutes and were then stained using the Giemsa stain method. Reagents were from Muto Pure Chemicals Co., Ltd, Tokyo, Japan. At least 400 non-squamous cells, including eosinophils, neutrophils, lymphocytes, macrophages and ciliated epithelial cells were counted differentially. Results were expressed as percentages of total non- squamous counts. If examination of slides revealed macrophages and ciliated epithelial cells, the sample was considered to be of bronchial origin and was included in the study. Cytospin slides for immunocytochemistry were processed immediately, or wrapped and stored at – 80℃ (at least two weeks) prior to fixation and permeabililization. It was confirmed that there is no effects of freezing and thawing on immunocytochemical results.

### Data Analysis

The values of lung function are expressed as mean ± standard deviation. Data of logPC20, exhaled nitric oxide concentration and sputum eosinophil ratio are expressed as mean (95% confidence interval (CI)). Differences were analyzed using Willcoxon signed rank test with the level of significance ($p$-value) set at 0.05.

## *RESULTS*

### EXHALED NITRIC OXIDE CONCENTRATION, PC20 AND SPUTUM EOSINOPHIL RATIO OF ALL PATIENTS

The pretreatment values of exhaled nitric oxide concentration, PC20 and sputum eosinophil ratio were 117 ± 95 ppb, 2.60 ± 0.59 mg/ml, and 13.1 ± 14.5%, respectively, for the 27 patients with mild intermittent asthma. Airway inflammation was certainly present even in these patients and the level of airway hyperresponsiveness was elevated (Fig. 1).

### TIME COURSE OF EXHALED NITRIC OXIDE CONCENTRATIONS IN THE BUD AND MK GROUPS

Before the treatment, no significant difference in exhaled nitric oxide concentrations was found between the BUD group and the MK group. The concentrations of the BUD group were 122 ± 89 ppb before the start of treatment, 60 ± 32 ppb after 1 month of treatment and 46 ± 24 ppb after 6 months of treatment. For the MK group, the concentrations were 112 ± 66 ppb before treatment, 78 ± 46 ppb after 1 month of treatment and 40 ± 18 ppb after 6 months of treatment. The exhaled nitric oxide concentrations were similarly lowered by treatment in both groups but not to the normal level. Degree of improvement measured by the reduction of exhaled nitric oxide concentration did not differ between the two groups according to analysis by unpaired t-test (Fig. 2).

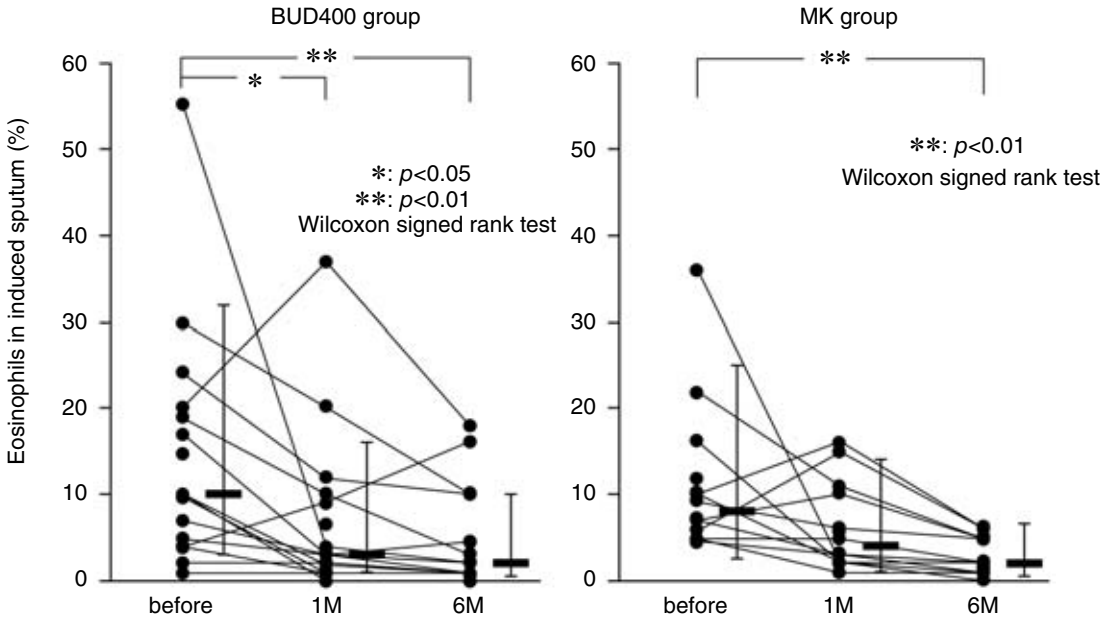


**Fig. 4** The time course of sputum eosinophil ratio in the BUD and MK groups. The ratios of eosinophils in the sputum of the BUD group ($n$ = 15) were significantly lowered after 1 and 6 months of treatment compared to pretreatment level, but did not return to the normal level. The ratios of eosinophils in the sputum of the MK group ($n$ = 12) were significantly lowered after 6 months of treatment compared to pretreatment level, but did not return to the normal level.

### TIME COURSE OF PC20 IN THE BUD AND MK GROUPS

There was no difference in pre-treatment PC20 between the BUD group and the MK group. The values of logPC20 for the BUD group were 2.47 ± 0.58 before treatment, 2.67 ± 0.47 after 1 month of treatment and 2.86 ± 0.52 after 6 months of treatment. For the MK group, these values were 2.76 ± 0.57 before treatment, 2.94 ± 0.71 after 1 month of treatment and 3.11 ± 0.62 after 6 months of treatment. In both groups, the values of logPC20 were not significantly improved after treatment (Fig. 3).

### TIME COURSE OF THE SPUTUM EOSINOPHIL RATIOS IN THE BUD AND MK GROUPS

Before the treatment, the percentage of sputum eosinophils did not differ between the BUD group and the MK group. Ratio in the BUD group were 14.5 ± 14.1% before treatment, 7.1 ± 9.9% after 1 month of treatment and 4.7 ± 5.8% after 6 months of treatment. The ratios in the MK group were 11.4 ± 9.2% before treatment, 6.3 ± 5.3% after 1 month of treatment 3.9 ± 2.2% after 6 months of treatment. The ratios of eosinophils were similarly improved but not to the normal level. The degrees of improvement in the percentage of sputum eosinophils did not differ between the two groups according to the analysis with the unpaired $t$-test (Fig. 4).

## *DISCUSSION*

According to guideline[1] of GINA 2002, anti-inflammatory therapy is not necessary for mild intermittent asthma (step 1), but in the Japanese guidelines[13] the use of a minimum dose of inhaled steroids is recommended. In the present study, the factor principally responsible for the elevation of airway hyperresponsiveness in mild asthma appeared to be eosinophilic inflammation, and if this is left untreated, it could induce airway remodeling and ultimately intractable asthma. It is generally believed that in asthma patients the longer the disease continues, the more remodeling of the airways, thickening of the basement membranes and hyperresponsiveness increase. Obase *et al.* reported, in a study of asthma patients who outgrew their condition, that the duration of infantile asthma is correlated with the duration of airway hyperresponsiveness and also with airway inflammation.[14] Although it is difficult to reverse structural changes which have been established as a result of advanced airway remodeling, it is quite likely that airway remodeling can be prevented by early introduction of anti-inflammatory treatment. Therefore, early intervention, *i.e.*, starting anti-inflammatory treatment in the early stage of development of asthma at step 1, is desirable.

Selroos *et al.* and Agertoft *et al.* reported that the introduction of inhaled steroid treatment in the early phase of development of asthma resulted in signifi-

cant improvement of respiratory function.[15,16] Haahtela *et al.* reported that early introduction of inhaled steroid treatment improved airway hyperresponsiveness.[17] These reports showed that respiratory function and hyperresponsiveness of patients whose duration of asthma was short responded well to inhaled steroids and that improvement was minimal in patients whose duration of asthma was long. Pauwels *et al.* reported in the inhaled steroids as regular therapy in early asthma (START) study that long-term administration of low-dose budesonide to patients with mild persistent asthma who had suffered from the disease for not longer than 2 years reduced the risk of asthma exacerbation and improved the control of asthm.[18] Sullivan *et al.* reported in the START study that early administration of budesonide reduced absence from school and lessened negative effects on work, and that the cost-effectiveness ratio of this treatment was also good.[19] There is a study of inhaled steroids and a leukotriene receptor antagonist for the airway inflammation in patients with step 1 and 2 mild asthma,[20] but data of patients with mild intermittent asthma (step 1) treated by leukotriene receptor antagonist alone have not been available. There is a clinical study by Kemp *et al.* on the effect of montelukast on exercise induced asthma in children with age of 6 to 14 years, but, in that study, only selective number of patients could fit in the category of patients with mild and intermittent type asthma.[21] Moreover, in their study, the short term effect (2 crossover periods of 2 days) of the leukotriene receptor antagonist for challenge induced asthma was discussed in patients with mild intermittent asthma ; the aim was not the same as that of this long term study.

In the present study, a conclusion was drawn from the results of the 6-month long-term treatment, in which early intervention of anti-inflammatory treatment was found to be necessary for patients with mild and intermittent asthma (step 1). In this study we did not analyze data from the point of view of disease duration because of the limited number of patients ; however, it appears that, even at step 1, lengthening of duration of asthma due to lack of or insufficient treatment leads to persistent airway inflammation and change of airway structures, *i.e.*, remodeling, resulting in persistent elevation of airway hyperresponsiveness. Therefore, it appears possible to normalize airway hyperresponsiveness by treatment of airway inflammation at an early phase of development of asthma. The present study was not conducted with comparison with placebo. Yet, we concluded that the improvement in airway inflammation was due to the treatment effects, but not the natural course of recovery process because we selected patients who had stable (step 1) asthma without attacks as subjects of the study, and those patients remained stable throughout the study period. In fact, those patients were in stable phase of asthma (step 1) according to patient diaries and measurements of peak flow ; no symptoms, use of inhaled β2 stimulant as needed and no changes in peak flow, and their asthma symptoms were well controlled during this study. The aim of this study was to evaluate the treatment for airway inflammation in stable step 1 asthmatic patients without asthma attacks. However, there were patients included in this study who received β2-stimulant alone, and those cases will be reported in the future. Although the definitions of cure and remission of asthma have not been clearly established, our study has indicated that most asthma patients who outgrew their disease have persistent airway inflammation and airway hyperresponsiveness,[14] and that there is a risk of asthma recurrence even if patients have had no symptoms for 10 years or longer. The patients in step 1 of the present study have levels of airway inflammation and airway hyperresponsiveness similar to those who outgrew their disease and, therefore, it is possible that their asthma symptoms will reappear in the future.

There is no doubt that anti-inflammatory treatment is now important in asthma therapy. Currently, inhaled steroids are the best medications, as safe and efficacious anti-inflammatory drugs that can be used for a long period of time. Reports published thus far have all suggested that prevention of airway remodeling is possible with the early introduction of inhaled steroid therapy. However, the present study revealed that, though it was difficult to distinguish the responder group from the non-responder group, leukotoriene receptor antagonist was also effective against step 1 asthma.

The main cause of increase in airway hyperresponsiveness is airway inflammation. Airway inflammation can be evaluated by collecting sputum induced by inhaled hyperosmotic NaCl solution and analyzing its cell and supernatant components. By determining the level of airway inflammation by measuring the number of eosinophils in induced sputum, ECP and cytokines, it is also possible to examine the relationship of airway inflammation with increases in airway hyperresponsiveness. Our plan for the future is to measure ECP and cytokines in the supernatant of sputum of these patients, perform immunostaining of the cells in sputum and investigate the cells that produce these substances. By testing the sputum induced by inhaled hyperosmotic NaCl solution and by introducing anti-inflammatory treatment while asthma is still at an early stage or is mild, it will be possible to improve airway hyperresponsiveness, prevent remodeling, prevent progression of disease to intractable asthma and, possibly, attain cure of asthma in certain cases.

In conclusion, even in mild intermittent asthma, exhaled nitric oxide concentrations and sputum eosinophil ratios were elevated and airway inflammation was clearly present. Airway hyperresponsiveness was

also elevated. The effects of low-dose inhaled steroid and leukotriene receptor antagonist in improving airway inflammationwere almost the same. Therefore, to prevent remodeling and disease progression to severe or intractable asthma, early introduction of anti-inflammatory treatment is necessary even in cases of mild intermittent asthma. We believe that either of the two types of medications, *i.e.*, low-dose inhaled steroids and leukotriene receptor antagonists, can be chosen as anti-inflammatory drugs for mild intermittent asthma.

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