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Efficacy of Mepolizumab for Long-term Treatment in Patients with Severe Asthma

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Abstract: Mepolizumab is a monoclonal antibody against interleukin-5 used for the treatment of severe asthma. The effect of long-term mepolizumab administration and its persistence in clinical practice is poorly understood. Thus, this study aimed to investigate the effect of long-term administration of mepolizumab in patients with severe asthma. Mepolizumab was administered to 20 patients with severe asthma. We then prospectively followed the patients for 104 weeks to investigate the efficacy of long-term mepolizumab administration in clinical practice. Eleven patients were evaluated for 104 weeks. Mepolizumab administration reduced asthma exacerbations in a year from 52 to 104 weeks and improved asthma control in every period as assessed by questionnaires. Also, blood eosinophil counts decreased at every point, and blood basophil counts decreased at 104 weeks. We compared various parameters among the 11 patients who continued administration for more than 104 weeks and 7 patients who discontinued treatment due to ineffectiveness. Significant differences were observed in disease duration, maximum expiratory flow at 50%, and blood basophil count. Long-term mepolizumab administration improved asthma symptoms in patients with severe asthma and reduced the frequency of exacerbations.

Key words: mepolizumab, anti-IL-5 antibody, eosinophilic asthma, severe asthma, eosinophil count

Introduction

Bronchial asthma is a disease characterized by eosinophilic airway inflammation and remodeling, which limit airflow. These changes involve allergic inflammation that leads to the release of inflammatory cytokines and chemokines[1-3]. The roles of several cytokines and chemokines in asthma have been elucidated[4-10]. Interleukin (IL)-5 is involved in the proliferation and migration of immature eosinophils in the bone marrow and in the activation of mature eosinophils, whereas IL-4 and IL-13 induce the production of immunoglobulin E (IgE) by B cells[4, 5].

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Approximately 300 million people worldwide are affected by asthma, with 5%−10% of these cases considered severe asthma, causing approximately 250,000 deaths annually[11–13]. Hence, alternative treatments for severe asthma are important. The American Thoracic Society/European Respiratory Society (ATS/ERS) guidelines define severe asthma as a condition requiring treatment with a long-acting l2 antagonist (LABA), leukotriene receptor antagonist (LTRA), or theophylline, in addition to high-dose inhaled corticosteroids (ICS) in the previous year, or requiring continuous oral corticosteroid (OCS) for more than half a year. However, these treatments still lead to poor asthma control[14]. Therefore, biologics have been recently developed as new therapeutic agents for severe asthma.

Biologics are molecularly targeted therapies, such as monoclonal antibodies and fusion proteins, created by molecular biology and genetic engineering techniques. Mepolizumab is a monoclonal antibody against IL-5 that specifically binds to IL-5 and blocks it from binding to the IL-5 receptor I-chain expressed on eosinophils. Mepolizumab suppresses eosinophil proliferation and reduces eosinophils in the blood, sputum, and airway mucosa[15]. In the first clinical trial, which was not limited to eosinophilic asthma, sputum eosinophils almost disappeared, but airway hyper-responsiveness did not improve at all[16]. In a subsequent clinical trial, Pavord *et al* intravenously administered three doses (75 mg, 250 mg, and 750 mg) of mepolizumab to patients with eosinophilic asthma for 52 weeks and found that the frequency of asthma exacerbations was suppressed[17]. Further, Ortega *et al* showed that mepolizumab reduced the frequency of asthma exacerbations at 32 weeks by 53% compared to the placebo group. Mepolizumab was also associated with improved pulmonary function, asthma control, and quality of life[18]. In another clinical trial, Bel *et al* reported a reduction of OCS dosage 24 weeks after treatment with mepolizumab[19]. Suppression of asthma exacerbation frequency and OCS dose reduction were observed after a 4-year course of mepolizumab[20]. Thus, the effects of mepolizumab on severe asthma have been shown in multiple clinical trials. However, the long-term effects of mepolizumab in the real world, which may include higher proportions of patients with poorly controlled asthma than those enrolled in previous clinical trials, remains unclear. Also, there are no clear indicators or biomarkers for identifying patients for whom biologic treatments are effective.

We investigated the long-term effects of mepolizumab in real-world patients with severe asthma and characterized the patients for whom this treatment would be effective.

Materials and methods

1 Patients

Twenty patients were enrolled in the study between August 2016 and October 2017. All enrolled patients were diagnosed with severe asthma by a physician, as defined according to the Japanese Asthma Prevention and Management Guideline 2015[21], and received treatment with high-dose ICS and one or more of the following additional medications: LABA, a long-acting muscarinic antagonist (LAMA), theophylline, LTRA, or OCS. Also, all patients had to have a blood eosinophil count of at least 150 cells/μl at screening or at least 300 cells/μl at some time during the previous year. Patients also demonstrated insufficient asthma control, which was

defined as at least one asthma exacerbation in the previous year that required treatment with systemic glucocorticoids for at least 3 days, visitation to an emergency department, or hospitalization. The study protocol was approved by the ethics committee of Showa University Hospital (approval date : July 28, 2016 ; approval No : 2108).

2 Methods

Mepolizumab was administered at a dose of 100 mg once every 4 weeks by subcutaneous injection. The intended treatment period was 104 weeks. The efficacy of mepolizumab treatment was assessed by pulmonary function tests, asthma control test (ACT) score, asthma control questionnaire (ACQ)-5 score, blood eosinophil count, blood basophil count, total IgE, fractional exhaled nitric oxide (FeNO), and the number of annual asthma exacerbations. An asthma exacerbation was defined as an asthma recurrence requiring administration of systemic glucocorticoids for at least 3 days by an attending physician, a visit to an emergency department, or hospitalization[22]. For each patient, the number of exacerbations during the 104 weeks was compared with that during the 52 weeks before the mepolizumab treatment. Pulmonary function tests were performed at 16, 52, and 104 weeks. The ACT score, ACQ-5 score, and FeNO were obtained at 16, 52, and 104 weeks. Blood eosinophil and basophil counts were measured at 16, 52, and 104 weeks, the data measured at 4 weeks before mepolizumab administration was set as baseline data.

Also, to search for an index that reflected the effects of mepolizumab, we compared the 11 patients who could continue mepolizumab administration for 104 weeks (long-term administration group) to the 7 patients who were unable to continue the administration (interruption group).

3 Statistical analysis

Statistical analysis of the treatment effect was performed using the Wilcoxon signed-rank test and Bonferroni correction for multiple comparisons. For group comparison, categorical variables were compared using Fisher's exact test, and continuous variables were compared using the Mann–Whitney U test. The analyses were performed using the JMP® software (SAS Institute, Japan, Tokyo, Japan). Data are expressed as median (interquartile range), and $P < 0.05$ indicated statistical significance. When we correct multiple comparisons with a Bonferroni test (P-value/6), only P-values less than 0.0083 (0.05/6) remained significant. Only in (Figure 1c), a P-value of < 0.0167 (0.05/3) was considered significant.

Results

1 Patients' characteristics

Of the 20 patients enrolled, 9 failed to continue treatment for the entire 104-week period : 7 stopped due to insufficient effect and 2 discontinued treatment due to adverse events. Of the 7 patients who stopped early, 6 patients had at least 2 exacerbations per year. One patient had continuous poor asthma control, and OCS could not be reduced. These patients discontinued mepolizumab for these reasons.

Adverse events that lead to treatment discontinuation were observed in two cases : one case

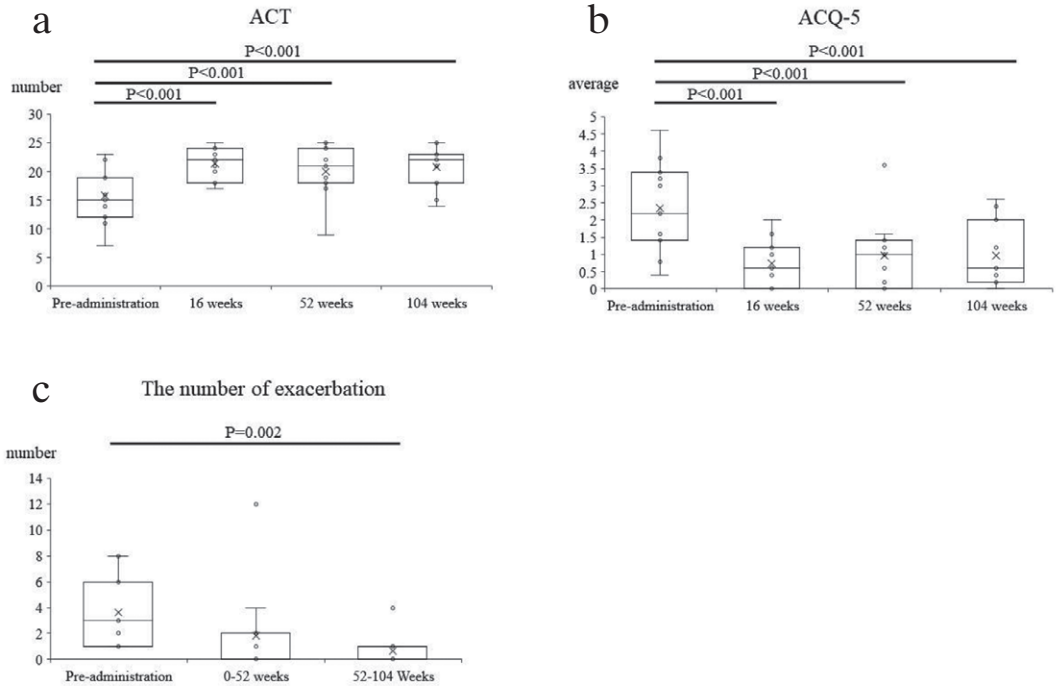

Fig. 1. Box plot showing changes in items related to asthma control improvement. (a) The change of ACT at baseline and after 16, 52, and 104 weeks of treatment. Preadministration indicates data 4 weeks before treatment. (b) The change of ACQ-5 at baseline and after 16, 52, and 104 weeks of treatment. Preadministration indicates data at 4 weeks before treatment. (c) The number of exacerbations at baseline and after 0–52 and 52–104 weeks of treatment. Only on (c), preadministration indicates data −52 to 0 weeks before treatment.
ACT : asthma control test, ACQ : asthma control questionnaire.

was discontinued due to pneumonia during mepolizumab administration. One case was discontinued owing to nausea and general malaise at the time of administration.

Therefore, 11 patients completed the study and were included in the analysis. The characteristics of the 11 patients upon enrollment are shown in Table 1. The mean ACT score was 15 ; however, 7 poorly controlled cases showed fewer than 20 points at the time of administration. Eleven patients received high-dose ICS and LABA. Five patients received LAMA, seven received LTRA, five received theophylline, and two received OCS. The comorbidities observed were allergic rhinitis (N = 8), eosinophilic sinusitis (N = 6), and eosinophilic otitis media (N = 5).

2 Comparison of patients' characteristics before treatment

The mean duration of asthma was significantly shorter in the long-term administration group than in the interruption group (Table 1). Pulmonary function tests revealed that the mean maximum expiratory flow at 50% ($\dot{V}_{50}$) value was significantly higher in the long-term administration group than in the interruption group (Table 1). There was no significant between-group difference in blood eosinophil count ; however, the long-term administration group tended to have a higher blood eosinophil count. The blood basophil count was significantly higher in the long-term administration group than in the interruption group (Table 1).

Table 1

Characteristic	Long-term administration group (N=11)	Interruption group (N=7)	P-value
Age (years)	60 (55-75)	64 (42-73)	0.52
Female sex — no. (%)	60 (54.5%)	6 (85.7%)	0.30
Body mass index	22.1 (21.5-26.2)	23.4 (21.7-24.0)	0.78
Former smoker — no. (%)	4 (36.3%)	1 (14.2%)	0.59
Duration of asthma (years)	14 (4-17)	39 (22-41)	< 0.01
Use of oral glucocorticoids — no. (%)	2 (18.1%)	3 (42.8%)	0.32
Number of exacerbations in the past year — no./patient	3 (1-6)	2 (2-6)	0.96
Allergic rhinitis — no. (%)	8 (72.7%)	3 (42.8%)	0.20
Eosinophilic sinusitis — no. (%)	6 (54.5%)	1 (14.2%)	0.08
Omalizumab use history — no. (%)	2 (18.1%)	2 (28.5%)	0.60
Score on ashma control test	15 (12-19)	14 (13-20)	1.00
Score on ashma control questionnaire-5 (average)	2.2 (1.4-3.4)	2.1 (1.4-2.3)	0.61
FVC (L)	2.39 (2.13-4.14)	2.32 (2.27-2.78)	0.85
FEV_1 (L)	1.72 (1.26-2.67)	1.16 (1-1.71)	0.10
$\dot{V}_{50}$ (L/sec)	1.34 (1.02-2.35)	0.51 (0.33-1.02)	0.04
$\dot{V}_{25}$ (L/sec)	0.3 (0.2-0.75)	0.19 (0.12-0.36)	0.31
Blood eosinophil count (cells/μl)	960 (444-2,040)	180 (92-830)	0.07
Blood basophil count (cells/μl)	67 (42-85)	20 (17-48)	0.04
IgE (U/ml)	348 (206-474)	213 (158-960)	0.52
FeNO (ppb)	62 (34-104)	49.5 (15-109.5)	0.54

Values are shown as median (interquartile range) unless otherwise indicated, and $P < 0.05$ was considered to indicate statistical significance.
FVC : forced vital capacity, FEV_1 : forced expiratory volume in 1 second, Ig : immunoglobulin, FeNO : fractional exhaled nitric oxide

3 Improved asthma control

The change in each item after mepolizumab administration is shown in Figure 1. The mean scores of the ACT and ACQ-5 showed significant changes compared with those at baseline at every time point (Fig. 1a, b). Moreover, there was a significant decrease in the number of clinically significant exacerbations between 52 weeks before mepolizumab administration and 52-104 weeks after administration (Fig. 1c).

4 Changes in pulmonary function

The pulmonary function test results did not show any significant improvements in forced vital capacity (FVC) or forced expiratory volume in one second (FEV_1) at any point (Fig. 2a, b). $\dot{V}_{50}$ and $\dot{V}_{25}$ also did not show any significant changes after mepolizumab administration (Fig. 2c, d).

5 Blood examination and FeNO measurement

Blood eosinophil count had significantly decreased by 16 weeks of mepolizumab administration

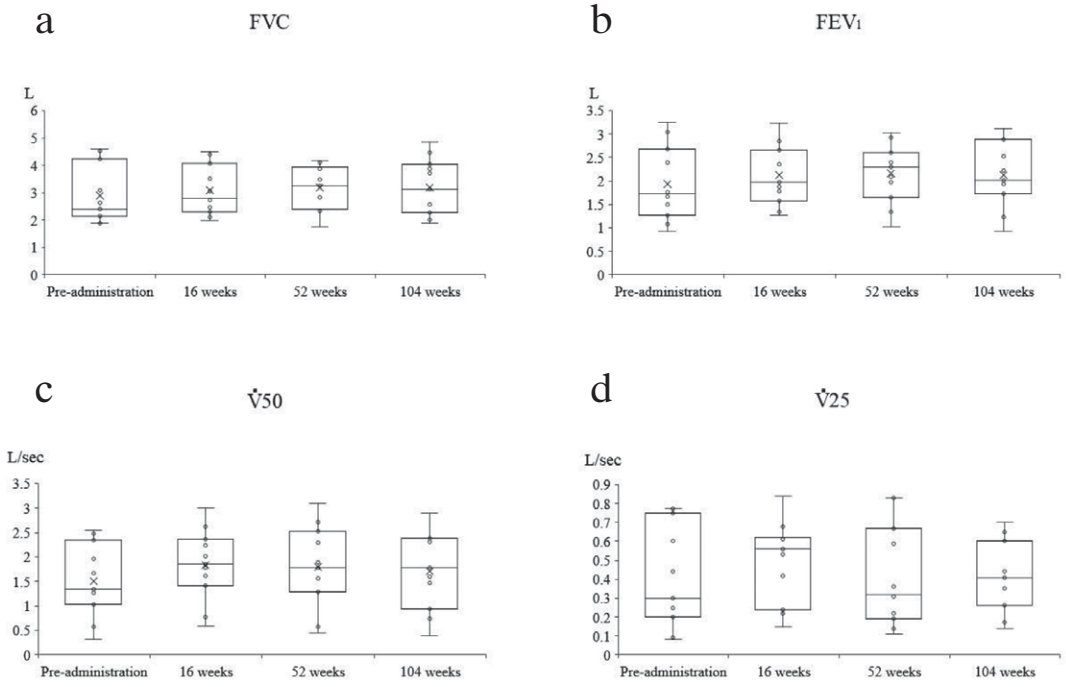

Fig. 2. Box plot showing changes in items related to pulmonary function. (a) The change of FVC at baseline and after 16, 52, and 104 weeks of treatment. (b) The change of FEV_1 at baseline and after 16, 52, and 104 weeks of treatment. (c) The change of $\dot{V}_{50}$ at baseline and after 16, 52, and 104 weeks of treatment. (d) The change of $\dot{V}_{25}$ at baseline and after 16, 52, and 104 weeks of treatment. Preadministration indicates data at 4 weeks before treatment.
FVC : forced vital capacity, FEV_1 : forced expiratory volume in 1 second.

and remained low for 104 weeks (Fig. 3a). Blood basophil count had also decreased significantly by 104 weeks of treatment (Fig. 3b). However, the mean value of FeNO was not decreased by mepolizumab treatment (Fig. 3c). Further, there was no significant change in serum total IgE throughout the 104 weeks (Fig. 3d).

Discussion

We investigated the efficacy and safety of long-term mepolizumab administration in clinical practice and characterized the patients for whom mepolizumab treatment was effective.

To examine symptom improvement by mepolizumab, we first measured ACT and ACQ-5 scores. Our results showed significant improvement in the ACT and ACQ-5 scores by 16 weeks of treatment with mepolizumab, with continued effects for 104 weeks. In a previous study, Bel *et al* showed that the ACQ-5 score improved 2 weeks after mepolizumab administration, and the effect continued for 24 weeks[19]. Moreover, Khatri *et al* showed that mepolizumab decreased the ACQ-5 score by 12 weeks, with persistent effects for more than 3 years[20]. These results were mostly consistent with our results. Thus, we expect that subjective symptoms will improve early after mepolizumab administration. This effect should be sustained.

From 52 to 104 weeks, there was a significant decrease in the number of annual exacerbations compared to the year before mepolizumab administration. The previous study showed a signifi-

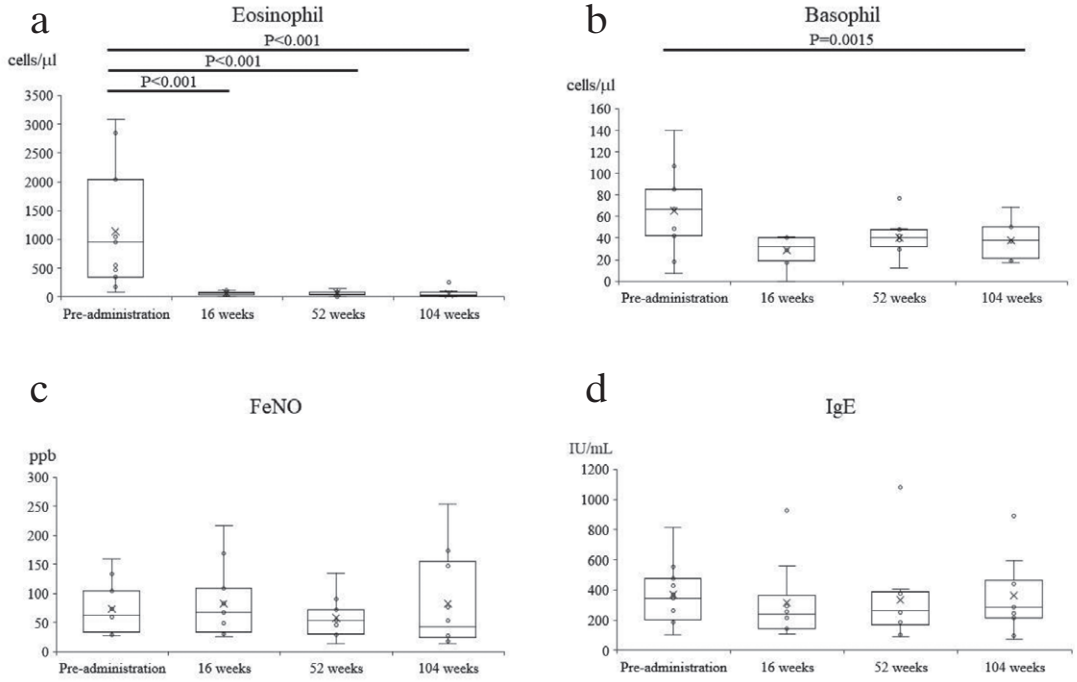

Fig. 3. Box plot showing changes in items related to a blood examination and FeNO measurement. (a) The change of eosinophils at baseline and after 16, 52, and 104 weeks of treatment. (b) The change of basophils at baseline and after 16, 52, and 104 weeks of treatment. (c) The change of FeNO at baseline and after 16, 52, and 104 weeks of treatment. (d) The change of serum IgE at baseline and after 16, 52, and 104 weeks of treatment. Preadministration indicates data at 4 weeks before treatment.
FeNO : fractional exhaled nitric oxide, Ig : immunoglobulin.

cant decrease in the number of exacerbations at 52 weeks[20]. In contrast, we did not find a significant reduction in the number of exacerbations at the same time point. This difference was probably caused by the smaller number of patients in this study. However, treatment continuation from 52 to 104 weeks significantly decreased the number of exacerbations compared to the year before mepolizumab administration. In this study, we evaluated patients with asthma who had been treated with mepolizumab for 104 weeks. Further, the patients' physicians had judged the treatment to be effective. The current recommendation is to evaluate the efficacy of mepolizumab within 1 year of treatment[23] ; however, evaluation after 1 year, even when the effect is unclear, may also be beneficial in real-world clinical practice.

Blood eosinophil counts significantly decreased at 16 weeks of mepolizumab treatment, and the effect was maintained for 104 weeks. Mepolizumab decreases eosinophil proliferation by binding to IL-5, inhibiting its binding to the IL-5 receptor α subunit expressed on eosinophils[15]. Our results also suggested that blood eosinophil count was decreased by mepolizumab through neutralization of IL-5, which promotes strong eosinophil activation and proliferation. In this study, blood eosinophil count tended to be higher in the long-term group. In other clinical studies, the higher the number of eosinophils, the higher the asthma exacerbation suppression rate, and the greater likelihood that blood eosinophil counts were associated with the effects of mepolizumab.

IL-5 is known as a cytokine required for basophil differentiation, and it enhances histamine release from basophils[24]. Consequently, mepolizumab administration inhibits IL-5 production, decreasing basophils.

Mepolizumab treatment did not inhibit FeNO production. One of the reasons was that the number of blood eosinophils was decreased by mepolizumab, but the number of eosinophils in the lung tissue remained, allowing FeNO production to continue. Recently, NO was thought to be produced by airway epithelial cells and inflammatory cells in the airway. It has also been reported that NO is produced by inducible nitric oxide synthase (iNOS), which is present in the airway epithelium via stimulation by Th2 cytokines, such as IL-4 and IL-13, but not IL-5[25]. Thus, IL-4 and IL-13 are considered main factors in FeNO production. In a clinical trial of dupilumab, which acts by blocking the IL-4/IL-13 receptor, FeNO production was significantly reduced in patients with asthma, suggesting that IL-4 and IL-13 are more involved in FeNO production IL-5[26].

To examine the effective group characteristics for mepolizumab treatment, we compared mepolizumab efficacy in the long-term administration and interruption groups. The Global Evaluation of Treatment Effectiveness recommends evaluation of the effect of omalizumab, an anti-IgE antibody, for patients with asthma through subjective evaluation of an attending physician[24]. Consistent with this recommendation, the patients in this study were divided into two groups based on the attending physician's evaluation, and various parameters were compared between the two groups. The results showed significant differences in the period from the onset of asthma, $\dot{V}_{50}$ value, and blood basophil count. Mepolizumab treatment was thus considered effective in patients shortly after the onset of asthma, which we expect is associated with less-severe airway inflammation and remodeling. Interestingly, we showed, for the first time, that IL-5 played an important role in the production of blood basophils. In a mouse model of asthma, basophils extend the life span of Th_2 cells and enhance Th_2 cytokine production[27]. Motomura *et al* showed that basophils prolong the lifespan of the innate lymphoid cell (ILC) 2 cells and enhance the production of Th_2 cytokines involved in eosinophilic inflammation[28]. Thus, basophils, which are closely related to airway inflammation, are considered to be associated with Th_2 cytokines, contributing to the efficacy of mepolizumab against asthma.

There were several limitations to this study. First, for long-term evaluation, the number of patients was small; thus, future studies with more patients are necessary. Second, as the investigators were unblinded, selection and measurement biases might have occurred.

In conclusion, this study confirmed the long-term efficacy of mepolizumab treatment for patients with severe eosinophilic asthma. Also, mepolizumab treatment was shown to be more effective for cases with short asthma morbidity and a large number of basophils. Future studies are required to investigate the effective phenotypes and biomarkers for treatment with mepolizumab.

Conflicts of interest disclosure

No potential conflict of interest was disclosed.

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