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Original Article

Clinical characteristics of patients with not well-controlled severe asthma in Japan: Analysis of the Keio Severe Asthma Research Program in Japanese population (KEIO-SARP) registry

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FAS, Full analysis set; FeNO, Fractional exhaled nitric oxide; FEV₁, Forced expiratory volume in 1 s; %FEV₁, Percent predicted FEV₁; GINA, Global Initiative for Asthma; ICS, Inhaled corticosteroids; IgE, Immunoglobulin E; IL, Interleukin; IRB, Institutional Review Board; KEIO-SARP, Keio Severe Asthma Research Program; LABA, Long-acting β_2 -agonist; OCS, Oral corticosteroids; SABA, Short-acting β_2 -agonist; SD, Standard deviation; TSLP, Thymic stromal lymphopoietin; USD, US dollars

ABSTRACT

Background: Multiple phenotypes exist within the classification of severe asthma. However, characteristics of patients with not well-controlled severe asthma have not been well identified.

Methods: Japanese patients with asthma (age ≥ 20 years) were enrolled at the Keio University Hospital and its affiliated hospitals in this observational study (Keio Severe Asthma Research Program). Among them, patients with severe asthma (those undergoing Global Initiative for Asthma [GINA] 2018 step 4 or 5 treatment) were included in this analysis and investigated clinical characteristics based on asthma control status.

Results: Of the 154 patients (men, 46.8%; age, 60.1 ± 14.9 years), 87 (56.5%) had not well-controlled (partly controlled and uncontrolled) asthma (GINA step 4, 42 patients; step 5, 45 patients). Overall, there were no significant differences in clinical characteristics between patients with well-controlled and not well-controlled asthma. However, cluster analysis revealed that distinct 5 clusters (cluster 1, well-controlled; cluster 2, eosinophilic; cluster 3, non-type 2 inflammation; cluster 4, high periostin; and cluster 5, late-onset type 2 inflammation), and clusters 2–5 were not well-controlled. Among them, cluster 3 was characterized by low eosinophil counts, low periostin levels, and less frequent olfactory disturbance, and this cluster had the worst asthma control.

Conclusions: Japanese patients with severe asthma were divided into well-controlled and not-well-controlled asthma, and we confirmed heterogeneity of not well-controlled severe asthma. These patients, especially non-type 2 phenotype, require a further therapeutic approach. (University Hospital Medical Information Network Clinical Trials Registry, UMIN000002980)

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Introduction

Asthma is a heterogeneous disease characterized by chronic airway inflammation and clinical symptoms based on variable expiratory airflow limitation (e.g., wheeze and shortness of breath) and cough.¹ As of 2017, approximately 2.7 billion persons worldwide had been affected by asthma.² The prevalence of severe asthma is estimated to be approximately 5%–10% of the entire asthma population.³ For example, the prevalence of severe asthma was reported to be 3.6% of all asthma patients in the Netherlands⁴ and 8.1% in Danish adult (age 18–44 years) patients.⁵ In Japan, according to a postal mail survey study,⁶ 10.6% of adult patients with asthma had severe asthma (asthma that requires high-dose inhaled corticosteroids [ICS] plus long-acting β_2 -agonists [LABAs] with additional controllers to prevent the disease from becoming uncontrolled or asthma that remains uncontrolled despite those therapies³). Moreover, a recent health insurance claims database study in Japan reported that 7.8% of patients with asthma (age 17–75 years) treated with ICS or ICS plus LABA had severe asthma.⁷

Although some patients with severe asthma are well controlled by current treatment, others are not controlled under current treatment and impose a burden on the healthcare system. According to the previous Japanese claims database study, Japanese severe asthma patients were further divided into 2.5% with uncontrolled and 5.3% with controlled asthma.⁷ Importantly, more patients with severe uncontrolled asthma (13.7%) required hospitalization than those with severe controlled asthma (6.2%) or mild to moderate asthma (3.0%). The mean annual medical expenses were also higher in patients with severe uncontrolled asthma (8346 US dollars [USD]) than in those with severe controlled asthma (5989 USD) or mild to moderate asthma (3422 USD).⁷ Hence, research is warranted to identify the characteristics of uncontrolled patients with severe asthma and to arrive at effective treatment options.

Previous research has highlighted several factors potentially associated with poor asthma control, such as eosinophilic asthma (eosinophils ≥ 150 –300 cells/ μ L),⁸ being overweight (body mass index [BMI] ≥ 25 kg/m²),⁹ higher age,¹⁰ improper inhaler technique,¹¹ poor compliance to medication,¹² respiratory infections,¹² and presence of animals inside the home.¹² Moreover, some research has been performed to identify the characteristics of severe asthma in Japan. For example, results of the Keio Severe Asthma Research Program (KEIO-SARP) study demonstrated that > 80% of Japanese patients with severe asthma were classified as type 2 asthma (peripheral eosinophils ≥ 300 cells/ μ L, serum periostin ≥ 95 ng/mL, or 1 or more perennial inhaled allergen-specific IgE concentrations > 0.70 UA/mL with total IgE 30–1500 IU/mL).¹³ However, further research is warranted to investigate biomarkers and clinical characteristics associated with poor asthma control in Japanese patients with severe asthma.

This study aimed to investigate the demographic and clinical characteristics of patients whose severe asthma was not well-controlled despite treatment by allergy or respiratory specialists in Japan. This study is registered at the University Hospital Medical Information Network Clinical Trials Registry (UMIN000002980).

Methods

Study design

The design of this observational KEIO-SARP study has been published previously.^{13,14} In brief, we enrolled Japanese patients

with asthma (age ≥ 20 years) at the Keio University Hospital and its affiliated hospitals (18 institutions in total) in a consecutive manner.^{13,14} A diagnosis of asthma was made by respiratory specialists. Patients with widespread lung disease or uncontrolled malignant tumors were excluded. Among the enrolled patients, those requiring step 4 or 5 treatment (as defined by the Global Initiative for Asthma 2018 [GINA 2018]¹⁵) to achieve optimal asthma control were defined as patients with severe asthma and included in this analysis. The ICS or oral corticosteroids (OCS) dose was based on the physician's decision, and no dose adjustments were required in this study. The clinical indices were measured under stable treatment at the time of enrollment.

The study protocol was initially approved by the Institutional Review Board (IRB) of the Keio University School of Medicine (IRB approval number: 20090009) and then subsequently approved by the IRB of each participating institution. This study was conducted in compliance with the Declaration of Helsinki. All patients provided written informed consent, and patient anonymity was preserved using methods approved by the IRB.

Study population

As described earlier, among the enrolled patients with asthma, those requiring GINA 2018 step 4 (middle- or high-dose ICS [fluticasone equivalent > 250 μ g/day] plus asthma controllers [LABA, leukotriene receptor antagonist, theophylline, or tiotropium]) or step 5 (step 4 plus omalizumab and/or continuous OCS) treatment were included in the full analysis set (FAS). The patient enrollment period was from April 2010 to April 2013, with database lock for this analysis in July 2017.

Study assessment at the time of enrollment

As reported previously, patient demographics and clinical characteristics, biomarker levels, and pulmonary function were assessed at the time of enrollment.^{14,16} Serum periostin levels were measured using the Human Periostin enzyme-linked immunosorbent assay kit (Shino-Test Corporation, Sagamihara, Japan). Serum levels of thymic stromal lymphopoietin (TSLP), IL-5, IL-13, and IL-33 were measured using the Quantikine enzyme-linked immunosorbent assay kits (R&D Systems, Minneapolis, MN, USA). Serum IL-4 and IL-6 levels were measured using the Bio-Plex® Suspension Array System (Bio-Rad Laboratories, Hercules, CA, USA). Serum total IgE levels were measured using a fluorescence enzyme immunoassay (Mitsubishi Chemical Medience Corporation, Tokyo, Japan).^{14,16} Pulmonary function was assessed using the CHESTAC-9800 spirometer (CHEST, Tokyo, Japan).^{14,16} Predicted forced expiratory volume in 1 s (FEV₁) was calculated using the lambda-mu-sigma method recommended for the Japanese population by the Japanese Respiratory Society.¹⁷ In addition, data on asthma symptoms, olfactory function, asthma history, and current asthma treatment were captured using a self-completed questionnaire. Patients were deemed as having olfactory disturbance if they selected “Yes” for the question “Do you feel any loss in the ability to smell?” in the questionnaire.

Data categorization

Patients were categorized as well-controlled and not well-controlled (i.e., partly controlled or uncontrolled) asthma as per the GINA 2018 criteria.¹⁵ In brief, patients meeting all 4 criteria (daytime asthma symptoms not more than twice a week, no night-

Table 1

Patient demographics and clinical characteristics at enrollment (FAS).

Characteristics	Overall (N = 154)	GINA step 4 (n = 87)	GINA step 5 (n = 67)
Age (years), mean $\pm$ SD	60.1 $\pm$ 14.9	60.1 $\pm$ 13.6	60.1 $\pm$ 16.6
Male	72 (46.8)	47 (54.0)	25 (37.3)
Height (cm), mean $\pm$ SD [†]	159.7 $\pm$ 8.7	161.3 $\pm$ 8.7	157.7 $\pm$ 8.2
Weight (kg), mean $\pm$ SD [†]	61.4 $\pm$ 12.8	61.6 $\pm$ 12.0	61.3 $\pm$ 14.0
BMI (kg/m ²), mean $\pm$ SD [†]	24.1 $\pm$ 4.6	23.6 $\pm$ 3.8	24.7 $\pm$ 5.4
Smoking status			
N	149	83	66
Never smoker	77 (51.7)	38 (45.8)	39 (59.1)
Former smoker	69 (46.3)	43 (51.8)	26 (39.4)
Current smoker	3 (2.0)	2 (2.4)	1 (1.5)
Brinkman index, mean $\pm$ SD [†]	431.5 $\pm$ 466.3	466.1 $\pm$ 458.2	375.7 $\pm$ 482.8
Age at asthma onset (years)			
N	141	81	60
Mean $\pm$ SD	34.3 $\pm$ 22.8	34.8 $\pm$ 20.8	30.5 $\pm$ 25.2
$\leq$ 15 years	41 (29.1)	17 (21.0)	24 (40.0)
> 15 years	100 (70.9)	64 (79.0)	36 (60.0)
Asthma duration (years), mean $\pm$ SD [‡]	26.4 $\pm$ 18.2	25.7 $\pm$ 17.2	29.3 $\pm$ 20.3
Average days with asthma symptoms			
N	145	80	65
None or $\leq$ 3 days per month	74 (51.0)	46 (57.5)	28 (43.1)
About 1 or 2 days a week	33 (22.8)	17 (21.3)	16 (24.6)
$\geq$ 3 days per week	22 (15.2)	10 (12.5)	12 (18.5)
Almost every day	16 (11.0)	7 (8.8)	9 (13.8)
Hospitalization for asthma attacks in the past 1 year			
N	143	78	65
Yes	42 (29.4)	16 (20.5)	26 (40.0)
Emergency room visit or outpatient visit (unscheduled) for asthma attacks in the past 1 year			
N	144	78	66
Yes	93 (64.6)	49 (62.8)	44 (66.7)
Family history of asthma			
N	140	78	62
Yes	82 (58.6)	49 (62.8)	33 (53.2)
Apnea-Hypopnea Index, mean $\pm$ SD [‡]	8.5 $\pm$ 9.3	10.0 $\pm$ 10.7	6.6 $\pm$ 6.9
Allergy to mites			
N	153	86	67
Yes	75 (49.0)	46 (53.5)	29 (43.3)
Allergy to animal dander			
N	150	85	65
Yes	30 (20.0)	20 (23.5)	10 (15.4)
Allergy to fungus			
N	152	87	65
Yes	53 (34.9)	33 (37.9)	20 (30.8)
Allergy to insect			
N	152	66	86
Yes	46 (30.3)	13 (19.7)	33 (38.4)

Data are represented as n (%) unless otherwise specified.

[†]n = 153, [‡]n = 68, [§]n = 141, [¶]n = 46 for the overall population.

BMI, body mass index; FAS, full analysis set; GINA, Global Initiative for Asthma; SD, standard deviation.

time awakenings due to asthma, reliever usage not more than twice a week, and no activity limitation due to asthma) in the past 4 weeks were defined as those with well-controlled asthma. Data on biomarkers, pulmonary function tests, and patient demographics and clinical characteristics were summarized by asthma control status (well-controlled or not well-controlled).

Serum total IgE levels were categorized into <30, 30–1500, and >1500 IU/mL, and absolute eosinophil counts were categorized into <150 and $\geq$ 150 cells/ μ L. Percent predicted FEV₁ (%FEV₁) was categorized into $\leq$ 80% and >80%.

Statistical analyses

Categorical variables were summarized as the number and percentage of patients, and continuous variables were summarized as mean and standard deviation (SD). Statistical differences were assessed using a chi-squared test, the Mann–Whitney U test, and the Fisher's exact test, with a 2-sided level of significance of 0.05. A hierarchical cluster analysis was performed using Ward's method with JMP version 14 (SAS Institute, Cary, NC, USA). All statistical

analyses were performed using SAS version 9.4 (SAS Institute) or JMP version 14 (SAS Institute).

Results

Patient demographics and characteristics

Of the 199 eligible patients, 154 patients on GINA step 4 or step 5 treatment were included in the FAS and 45 patients were excluded. Reasons for exclusion were no asthma controllers received (n = 10), no ICS or asthma controllers received (n = 3), low ICS dose (n = 11), and low ICS dose and no asthma controllers received (n = 21).

Of the overall population (154 patients), 46.8% were men (72 patients), and the age was 60.1 $\pm$ 14.9 years (mean $\pm$ SD). Of the 149 patients with available smoking status data, nearly half (48.3%, 72 patients) were former or current smokers. The disease duration was 26.4 $\pm$ 18.2 years (mean $\pm$ SD). Among 145 patients with available data on average days with asthma symptoms, 16 (11.0%) had asthma symptoms almost every day. Among 140 patients with available data on family history of asthma, 82 (58.6%) had a family history

Table 2
Type of asthma treatment (FAS).

Characteristics	Overall (N = 154)	GINA step 4 (n = 87)	GINA step 5 (n = 67)
ICS	154 (100.0)	87 (100.0)	67 (100.0)
Mean $\pm$ SD dose (μ g/ day)	758.6 $\pm$ 294.1	773.3 $\pm$ 289.9	739.1 $\pm$ 300.7
OCS	55 (35.7)	0 (0.0)	55 (82.1)
Mean $\pm$ SD dose (mg/ day) [†]	7.7 $\pm$ 6.4	NA	7.7 $\pm$ 6.4
Omalizumab	20 (13.0)	0 (0.0)	20 (29.9)
SABA	141 (91.6)	78 (89.7)	63 (94.0)
None or $\leq$ 3 days per month	86 (61.0)	55 (70.5)	31 (49.2)
About 1 or 2 days a week	16 (11.3)	10 (12.8)	6 (9.5)
$\geq$ 3 days per week	11 (7.8)	2 (2.5)	9 (14.3)
Almost every day	28 (19.9)	11 (14.1)	17 (27.0)
LABA	128 (83.1)	66 (75.9)	62 (92.5)
Asthma controller (except LABA)	138 (89.6)	76 (88.4)	62 (92.5)
Theophylline	87 (56.5)	40 (46.0)	47 (70.2)
Leukotriene receptor antagonist	126 (81.8)	68 (78.2)	58 (86.6)
Long-acting muscarinic antagonists	22 (14.3)	14 (16.1)	8 (12.0)

Data are represented as n (%) unless otherwise specified.

FAS, full analysis set; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids; LABA, long-acting β_2 -agonist; NA, not applicable; OCS, oral corticosteroids; SABA, short-acting β_2 -agonist; SD, standard deviation.

[†] Prednisolone equivalent.

(Table 1). The serum total IgE level was high (730.6 $\pm$ 1972.8 IU/mL) and pulmonary function was reduced (FEV₁, 63.7% $\pm$ 14.2%; %FEV₁, 79.0% $\pm$ 23.3%) (Supplementary Table 1).

The percentage of former or current smokers was lower among patients on GINA step 5 treatment (40.9%) compared with those on GINA step 4 treatment (54.2%); the Brinkman index was also lower in patients on GINA step 5 treatment (mean $\pm$ SD, 375.7 $\pm$ 482.8) compared with those on GINA step 4 treatment (mean $\pm$ SD, 466.1 $\pm$ 458.2). The age at asthma onset was lower in patients on GINA step 5 treatment (age at onset, 30.5 $\pm$ 25.2 years; patients with onset at $\leq$ 15 years of age, 40.0%) compared with those on GINA step 4 treatment (age at onset, 34.8 $\pm$ 20.8 years; patients with onset at $\leq$ 15 years of age, 21.0%). The percentages of patients reporting asthma symptoms almost every day and those hospitalized for asthma attacks in the past 1 year were higher among those on GINA step 5 treatment (13.8% and 40.0%, respectively) compared with those on GINA step 4 treatment (8.8% and 20.5%, respectively) (Table 1). The serum total IgE level was lower in patients on GINA step 5 treatment (mean $\pm$ SD, 408.4 $\pm$ 449.5 IU/mL) than in those on GINA step 4 treatment (mean $\pm$ SD, 979.9 $\pm$ 2576.7 IU/mL) (Supplementary Table 1).

Type of asthma treatment

In the overall population, patients received an ICS dose of 758.6 $\pm$ 294.1 μ g/day. Omalizumab was used by 20 of 154 patients (13.0%). Among 141 patients using short-acting β_2 -agonists (SABAs), 28 (19.9%) had used the drug almost every day. Among 67 patients on GINA step 5 treatment, OCS were used by 55 (82.1%) patients (mean $\pm$ SD dose, 7.7 $\pm$ 6.4 mg/day) (Table 2). Omalizumab was used by 20 (29.9%) patients on GINA step 5 treatment. The percentages of patients using SABAs, LABAs, and asthma controllers (except LABAs) were higher in the GINA step 5 treatment group (94.0%, 92.5%, and 92.5%, respectively) than in the GINA step 4 treatment group (89.7%, 75.9%, and 88.4%, respectively) (Table 2).

Characteristics of well-controlled and not well-controlled asthma

Of the 154 patients included in the FAS, 67 (43.5%) were those with well-controlled asthma. Forty-one patients were those with partly controlled asthma and 46 were those with uncontrolled asthma, resulting in 87 (56.5%) patients with not well-controlled asthma (GINA step 4, 42 patients; step 5, 45 patients). The percentages of patients hospitalized for an asthma attack in the past 1 year were significantly higher ($P = 0.037$) in patients with not well-controlled asthma (36.8%) than in those with well-controlled asthma (20.9%) (Supplementary Table 2).

No significant difference was observed in terms of age at registration, age at asthma onset, and asthma duration between patients with well-controlled asthma and patients with not well-controlled asthma, indicating no clear association between asthma control status and aging. No significant difference was observed in the ICS dose between patients with well-controlled asthma and patients with not well-controlled asthma, while the proportion of patients using omalizumab was significantly higher in those with not well-controlled asthma vs. those with well-controlled asthma (18.4% vs. 6.0%, $P = 0.029$) (Supplementary Table 3). The percentages of patients with absolute eosinophil count <150 cells/ μ L were marginally but not significantly higher ($P = 0.055$) in patients with not well-controlled asthma (30.0%) compared with those with well-controlled asthma (16.1%) (Fig. 1). Likewise, the percentages of patients with %FEV₁ $\leq$ 80% were marginally but not significantly higher ($P = 0.092$) in patients with not well-controlled asthma (57.7%) compared with those with well-controlled asthma (43.1%) (Fig. 1). No statistically significant differences were observed in the mean cytokine levels (IL-4, IL-5, IL-6, IL-13, IL-33, and TSLP) between patients with well-controlled and not well-controlled asthma (Supplementary Table 3). Overall, no clear patient characteristics were found that was unique to those patients with not well-controlled severe asthma.

Cluster analysis

In view of the heterogeneity of the asthma phenotypes, we performed a cluster analysis to determine whether there were any independent patient groups representative of the characteristics identified in our analysis. GINA treatment step, asthma control, asthma attacks in the past 1 year (as a measure of asthma exacerbation), absolute eosinophil count, periostin level, and olfactory disturbance were used as variables. Of the 154 patients, 137 patients were included in the cluster analysis, because there are incomplete data sets in 17 patients (Fig. 2).

As a result, 5 distinct clusters were identified (cluster 1, well-controlled; cluster 2, eosinophilic; cluster 3, non-type 2 inflammation; cluster 4, high periostin; and cluster 5, late-onset type 2 inflammation). Among the 5 clusters, cluster 3 had non-type 2 inflammation as a phenotype and was characterized by low eosinophil counts, low periostin levels, less frequent olfactory disturbance, and worst asthma control among 5 clusters. The proportion of patients on GINA step 5 treatment was higher in cluster 3 compared with the other clusters (66.7% vs. 21.8%–65.5%, $P < 0.001$). The proportion of patients with olfactory disturbance was lower in cluster 3 compared with the other clusters (3.3% vs. 17.2%–53.3%, $P < 0.001$) although the mean OCS dose was similar across all clusters (5.2–9.8 mg/day, $P = 0.489$) (Table 3).

Discussion

We examined the clinical characteristics potentially associated with patients with not well-controlled severe asthma in Japan. Notably, more than half (56.5%) of patients on GINA step 4 and step

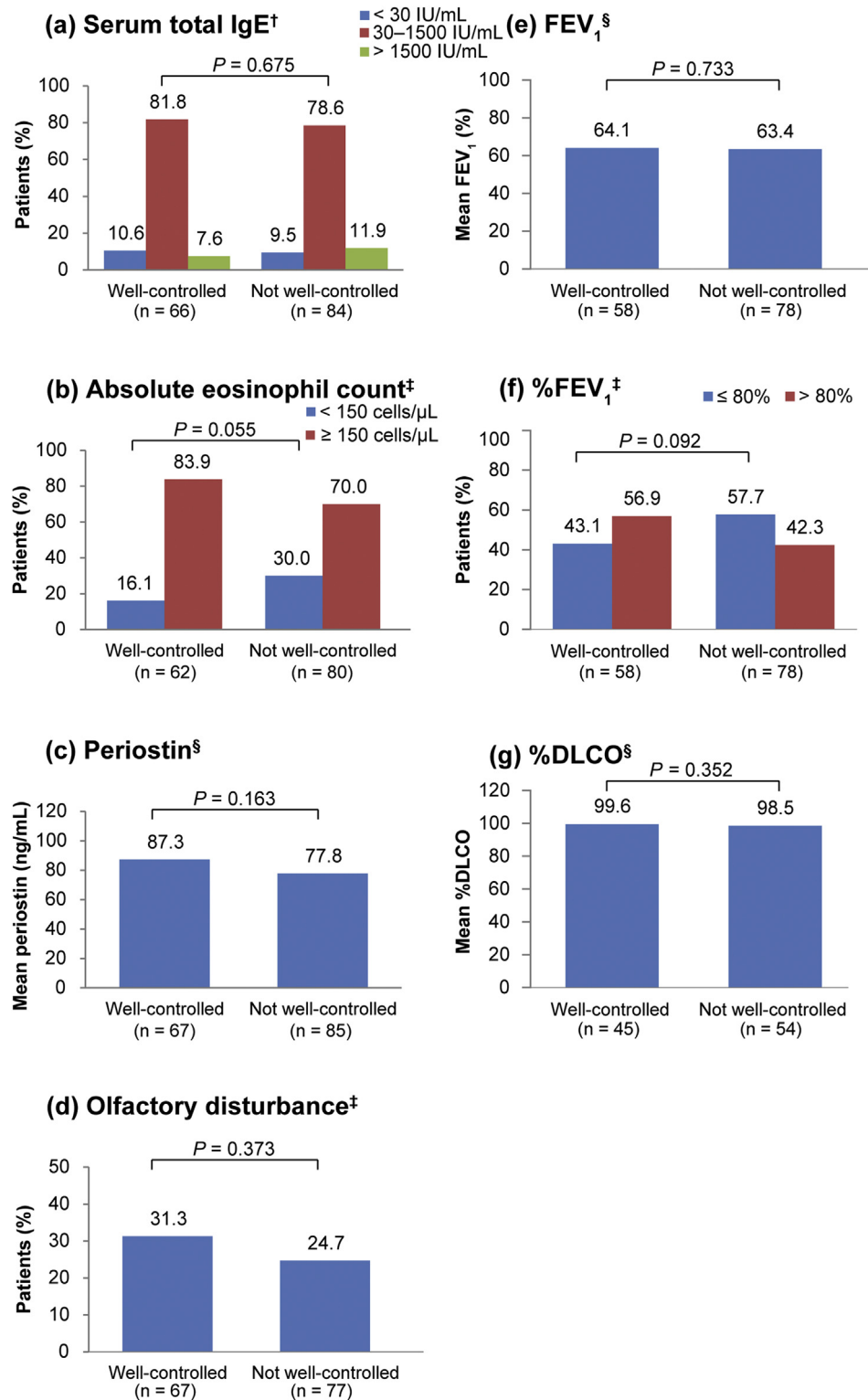


Fig. 1. Statistical comparison of (a) serum total IgE, (b) absolute eosinophil count, (c) mean periostin level, (d) presence of olfactory disturbance, (e) mean FEV₁, (f) %FEV₁, and (g) mean %DLCO between patients with well-controlled and not well-controlled asthma (FAS).

5 treatment included in our study had not well-controlled asthma despite treatment by allergy or respiratory specialists. Our cluster analysis revealed that five distinct phenotypes, which include one well-controlled phenotype and four not well-controlled phenotypes. Among them, a substantial number of patients was non-type

2 inflammation phenotype, which showed the worst asthma control.

Several factors have been found to be associated with poor asthma control, including eosinophilic asthma,⁸ higher BMI,⁹ higher age,¹⁰ respiratory infections,¹² and presence of animals

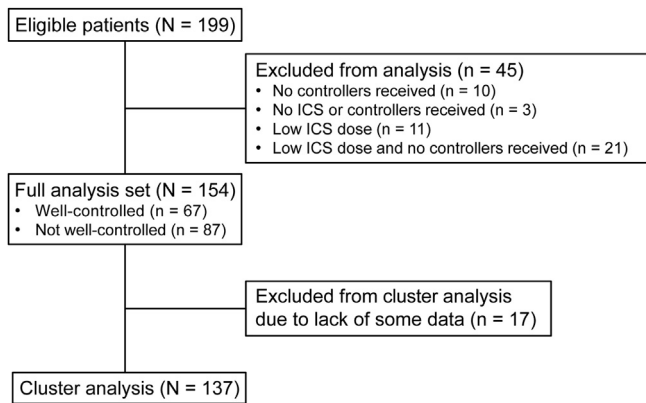


Fig. 2. Patient disposition. GINA, Global Initiative for Asthma; ICS, inhaled corticosteroids. [†]Fisher's exact test, [‡]Chi-squared test, [§]Mann–Whitney U test. %DL_{CO}, percent predicted diffusing capacity of the lungs for carbon monoxide; %FEV₁, percent predicted forced expiratory volume in 1 s; FAS, full analysis set; FEV₁, forced expiratory volume in 1 s; IgE, immunoglobulin E.

inside the home.¹² However, no statistically significant difference was observed in blood eosinophil count, BMI, or presence of pets at home between patients with not well-controlled and well-controlled asthma in our study. Because severe asthma is a heterogeneous population of various phenotypes, different factors for each phenotype may be involved in poor asthma control. In other words, statistical differences observed in the previous studies likely depend on the sample size within each cluster in severe asthma. Therefore, we decided to perform a cluster analysis to examine the characteristics of uncontrolled severe asthma.

Five distinct phenotypes were identified in our cluster analysis. Cluster 1 is a “well-controlled” phenotype, and the majority of patients included cluster 1 were well-controlled on GINA step 4 treatment. In contrast, more than half of the patients included in

clusters 2–5 were poorly controlled, and cluster 2–5 were further divided into “type 2 inflammation” phenotypes and “non-type 2 inflammation” phenotypes. Clusters 2, 4, and 5 were “type 2 inflammation” phenotypes, among which cluster 4 had high levels of periostin, a biomarker for IL-13 production. Cluster 5 was a relatively late-onset of asthma with a higher frequency of olfactory disturbances. Although our study did not investigate aspirin exacerbated respiratory disease, it has been previously reported that late-onset type 2 inflammation phenotype has a higher frequency of nasal polyps and aspirin exacerbated respiratory disease. In contrast, cluster 3 of non-type 2 inflammation had low eosinophil counts and periostin levels, and all cases were poorly controlled. Cluster 3 phenotype also had the highest rate of emergency room visits and asthma attacks, even though many patients were receiving GINA step 5 treatment. These findings demonstrated that there were well-controlled and poorly-controlled groups among patients with severe asthma, and the poorly controlled patients were further divided into “type 2 inflammation” and “non-type 2 inflammation” phenotypes, with the “non-type 2 inflammation” phenotype having the worst asthma control.

For improved asthma control in patients with not-well-controlled severe asthma, therapeutic approaches may need to be reconsidered. Results from randomized studies of omalizumab, mepolizumab, benralizumab, and dupilumab showed that reduction in asthma exacerbations with these antibodies was greater in patients with type 2 inflammation.^{18–21} However, there are no effective biologics for patients with non-type 2 inflammation. In recent years, clinical trials using anti-TSLP antibodies have shown the potential to be effective in both type 2 inflammation and non-type 2 inflammation, and the results of future clinical trials are expected.²² In addition, as the lower eosinophil count and lower periostin level may be partly due to the concomitant use of OCS and Omalizumab, obtaining eosinophil and periostin data before initiation of OCS may enable identification of patients for whom mepolizumab, benralizumab, and dupilumab could be effective

Table 3
Results of the cluster analysis.

Characteristics	Cluster 1 (N = 55)	Cluster 2 (N = 29)	Cluster 3 (N = 30)	Cluster 4 (N = 8)	Cluster 5 (N = 15)	P value
Phenotype	Well-controlled	Eosinophilic	Non-type 2 inflammation	High periostin	Late-onset type 2 inflammation	
Age (years), mean ± SD	61.7 ± 12.9	62.9 ± 15.6	54.5 ± 16.5	64.6 ± 9.5	65.4 ± 12.5	0.071 [†]
Male, n (%)	27 (49.1)	15 (51.7)	12 (40.0)	5 (62.5)	5 (33.3)	0.585 [‡]
BMI (kg/m ²), mean ± SD	24.0 ± 4.6	23.4 ± 3.9	26.3 ± 6.3	23.1 ± 2.6	22.6 ± 2.2	0.054 [†]
Age at asthma onset (years), mean ± SD	33.5 ± 23.3	35.7 ± 18.2	22.3 ± 25.7	43.5 ± 21.0	46.4 ± 18.5	0.011 [†]
Emergency room visit or outpatient visit (unscheduled) for asthma attacks in the past 1 year						
Yes, n (%)	30 (54.6)	21 (72.4)	25 (83.3)	4 (50.0)	8 (53.3)	0.053 [‡]
Asthma attacks in the past 1 year						
Yes, n (%)	37 (67.3)	26 (89.7)	30 (100.0)	8 (100.0)	13 (86.7)	<0.001 [‡]
Olfactory disturbance						
Yes, n (%)	20 (36.4)	5 (17.2)	1 (3.3)	4 (50.0)	8 (53.3)	<0.001 [‡]
GINA step 5						
Yes, n (%)	12 (21.8)	19 (65.5)	20 (66.7)	5 (62.5)	6 (40.0)	<0.001 [‡]
Not well-controlled						
Yes, n (%)	9 (16.4)	20 (69.0)	30 (100.0)	4 (50.0)	10 (66.7)	<0.001 [‡]
Serum total IgE (IU/mL), mean ± SD	503.1 ± 529.8	544.8 ± 564.4	619.9 ± 1551.6	1260.6 ± 1350.2	1884.6 ± 5573.3	0.191 [†]
Absolute eosinophil count (cells/μL), mean ± SD	316.6 ± 231.3	448.7 ± 212.4	125.7 ± 110.1	437.6 ± 204.6	1655.5 ± 682.2	<0.001 [†]
Periostin (ng/mL), mean ± SD	66.3 ± 16.8	102.5 ± 21.6	48.9 ± 13.7	209.5 ± 47.7	91.5 ± 27.8	<0.001 [†]
Use of OCS and omalizumab						
OCS, n (%)	10 (18.2)	17 (58.6)	17 (56.7)	5 (62.5)	6 (40.0)	<0.001 [‡]
OCS dose (mg/day), mean ± SD	5.2 ± 2.2	9.1 ± 8.3	7.2 ± 4.7	9.8 ± 9.4	5.7 ± 3.9	0.489 [†]
Omalizumab, n (%)	2 (3.6)	6 (20.7)	7 (23.3)	1 (12.5)	1 (6.7)	0.050 [‡]

BMI, body mass index; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; OCS, oral corticosteroids; SD, standard deviation.

[†] Mann-Whitney U test.

[‡] Fisher's exact test.

treatment options. For adult (age ≥ 18 years) patients with severe asthma, bronchial thermoplasty performed by certified bronchoscopy specialists is recommended in the Japanese 2018 asthma guidelines (treatment step 4), and may be considered as a treatment option.²³

This study has some limitations. First, none of the patients in this study had received mepolizumab, benralizumab, or dupilumab due to their relatively new launch in Japan (2016–2018). Second, the effects of inhaler techniques or drug adherence were not considered, although they are major factors associated with poor asthma control.^{11,12}

In conclusion, more than half of the patients with severe asthma included in our study had not well-controlled asthma, despite management by allergy or respiratory specialists. As the phenotype of not-well controlled severe asthma is heterogeneous, consideration of patient characteristics is necessary for the appropriate selection of therapeutic approaches, including monoclonal antibody therapies, in treating patients with not well-controlled asthma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.alit.2020.06.002>.

Conflict of interest

JM received a research grant from GSK Japan. KI received research funding from Shino-Test. KA received honoraria from Astellas Pharma, Boehringer Ingelheim, Kyorin Pharmaceutical, MSD, Novartis Pharma, and AstraZeneca. KF received honoraria from Boehringer Ingelheim and AstraZeneca. The rest of the authors have no conflict of interest.

Authors' contributions

TT, HK, and KF designed the study and wrote the manuscript. TT, HK, KM, JM, TM, MM, SO, MK, RW, YS, KS, and KA contributed to data collection. KI contributed to periostin measurement. TT and HK performed statistical analyses and interpretation of the results. All authors have read and approved the final manuscript.

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Supplementary materials

Supplementary Table 1

Biomarkers and pulmonary function parameters at enrollment (FAS).

Characteristics	Overall	GINA step 4	GINA step 5
	(N = 154)	(n = 87)	(n = 67)
Serum total IgE (IU/mL) [†]	730.6 ± 1972.8	979.9 ± 2576.7	408.4 ± 449.5
Absolute eosinophil count	480.8 ± 532.9	487.4 ± 497.5	412.9 ± 570.1
(cells/μL) [‡]			
Absolute lymphocyte count	2.45 ± 0.88 × 10 ⁶	2.61 ± 0.91 × 10 ⁶	2.28 ± 0.85 × 10 ⁶
(cells/μL) [§]			
Periostin (ng/mL) [¶]	82.0 ± 42.3	81.8 ± 44.1	82.2 ± 40.0
Filaggrin gene mutation positive			
n	127	68	59
Yes, n (%)	11 (8.7)	6 (8.8)	5 (8.5)
IL-4 (pg/mL)	13.8 ± 8.6	14.0 ± 8.3	13.5 ± 8.9
IL-5 (pg/mL)	36.8 ± 21.3	37.3 ± 20.9	36.2 ± 22.0
IL-6 (pg/mL)	84.5 ± 56.0	83.1 ± 52.0	86.2 ± 61.1
IL-13 (pg/mL)	20.5 ± 27.7	23.0 ± 34.4	17.4 ± 15.5
IL-33 (pg/mL) [#]	406.5 ± 957.9	376.4 ± 1042.0	445.0 ± 845.7
TSLP (pg/mL) [#]	11.6 ± 20.0	9.6 ± 10.1	14.1 ± 27.9
FEV ₁ (%) ^{††}	63.7 ± 14.2	63.3 ± 13.6	64.3 ± 15.1
%FEV ₁ ^{††}	79.0 ± 23.3	80.8 ± 28.1	68.7 ± 26.1
%DL _{CO} ^{‡‡}	99.0 ± 28.0	101.4 ± 27.3	95.6 ± 28.8

Data are represented as mean ± SD unless otherwise specified.

[†]n = 148, [‡]n = 142, [§]n = 29, [¶]n = 152, ^{||}n = 131, [#]n = 132, ^{††}n = 136, ^{‡‡}n = 99, and ^{§§}n = 64 for the overall population.

%DL_{CO}, percent predicted diffusing capacity of the lungs for carbon monoxide; %FEV₁, percent predicted forced expiratory volume in 1 second; FAS, full analysis set;; FEV₁, forced expiratory volume in 1 second; GINA, Global Initiative for Asthma; IgE, immunoglobulin E; IL, interleukin; SD, standard deviation; TSLP, thymic stromal lymphopoietin

Supplementary Table 2

Statistical comparison of demographic and characteristic parameters between patients with well-controlled and not wellcontrolled asthma (FAS).

Characteristics	Overall (N = 154)		<i>P</i> value
	Well-controlled (n = 67)	Not well-controlled (n = 87)	
Age at registration (years)			
Mean ± SD	62.3 ± 12.2	58.5 ± 16.6	0.347 [†]
Sex			
N	67	87	
Male, n (%)	30 (44.8)	42 (48.3)	0.666 [‡]
Female, n (%)	37 (55.2)	45 (51.7)	
BMI (kg/m ²)			
N	67	86	
Mean ± SD	23.7 ± 4.4	24.4 ± 4.7	0.361 [†]
Smoking status			
N	67	82	
Former/current, n (%)	34 (50.7)	38 (46.3)	0.592 [‡]
Never, n (%)	33 (49.3)	44 (53.7)	
Age at asthma onset (years)			
N	66	75	
Mean ± SD	35.5 ± 22.2	29.9 ± 22.3	0.156 [†]
≤ 15 years, n (%)	15 (22.7)	26 (34.7)	0.119 [‡]
> 15 years, n (%)	51 (77.3)	49 (65.3)	

Asthma duration (years)				
N	66	75		
Mean $\pm$ SD	25.7 $\pm$ 19.5	28.5 $\pm$ 17.8		0.204 [†]
Atopic asthma				
N	43	50		
Yes, n (%)	41 (95.3)	49 (98.0)		0.594 [§]
No, n (%)	2 (4.7)	1 (2.0)		
Hospitalization for asthma attacks in past 1 year				
N	67	76		
Yes, n (%)	14 (20.9)	28 (36.8)		0.037 [‡]
No, n (%)	53 (79.1)	48 (63.2)		
Emergency room visit or outpatient visit (unscheduled) for asthma attacks in past 1 year				
N	67	77		
Yes, n (%)	40 (59.7)	53 (68.8)		0.253 [‡]
No, n (%)	27 (40.3)	24 (31.2)		
Family history of asthma				
N	65	75		
Yes, n (%)	41 (63.1)	41 (54.7)		0.314 [‡]
No, n (%)	24 (36.9)	34 (45.3)		
Pets at home				
N	61	74		
Yes, n (%)	15 (24.6)	16 (21.6)		0.683 [‡]
No, n (%)	46 (75.4)	58 (78.4)		
Pulmonary diseases other than asthma				
N	61	74		
Yes, n (%)	18 (29.5)	22 (29.7)		0.978 [‡]
No, n (%)	43 (70.5)	52 (70.3)		
Sinusitis				
N	66	77		
Yes, n (%)	26 (39.4)	30 (39.0)		0.958 [‡]

No, n (%)	40 (60.6)	47 (61.0)	
Rhinitis			
N	67	79	
Yes, n (%)	42 (62.7)	56 (70.9)	0.293 [‡]
No, n (%)	25 (37.3)	23 (29.1)	
Reflux esophagitis			
N	67	76	
Yes, n (%)	9 (13.4)	14 (18.4)	0.418 [‡]
No, n (%)	58 (86.6)	62 (81.6)	
Sleep apnea syndrome			
N	67	76	
Yes, n (%)	7 (10.4)	6 (7.9)	0.596 [‡]
No, n (%)	60 (89.6)	70 (92.1)	
Use of ICS and omalizumab			
N	66	75	
ICS dose (µg/day), mean ± SD	731.0 ± 290.8	780.0 ± 296.6	0.377 [†]
Omalizumab use, n (%)	4 (6.0)	16 (18.4)	0.029 [§]

[†]Mann-Whitney U test. [‡]Chi-squared test. [§]Fisher's exact test.

BMI, body mass index; FAS, full analysis set; GINA, Global Initiative for Asthma; ICS, inhaled corticosteroid; SD, standard deviation.

Supplementary Table 3

Statistical comparison of cytokine levels between patients with well-controlled and not well-controlled asthma (FAS).

Characteristics	Overall (N = 154)		<i>P</i> value [†]
	Well- controlled (n = 67)	Not well- controlled (n = 87)	
IL-4 (pg/mL)			
N	58	73	
Mean ± SD	14.2 ± 7.8	13.4 ± 9.1	0.400
IL-5 (pg/mL)			
N	58	73	
Mean ± SD	38.1 ± 18.7	35.8 ± 23.2	0.246
IL-6 (pg/mL)			
N	58	73	
Mean ± SD	90.1 ± 53.9	80.0 ± 57.5	0.235
IL-13 (pg/mL)			
N	58	73	
Mean ± SD	20.6 ± 20.7	20.4 ± 32.4	0.374
IL-33 (pg/mL)			
N	59	73	
Mean ± SD	386.1 ± 946.5	423.0 ± 973.1	0.637
TSLP (pg/mL)			
N	59	73	
Mean ± SD	13.2 ± 28.1	10.2 ± 9.5	0.395

[†]Mann-Whitney U test.

FAS, full analysis set ; IL, interleukin; SD, standard deviation; TSLP, thymic stromal lymphopoietin.