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ORIGINAL RESEARCH

Characterization of Severe Uncontrolled Asthma in Japan: Analysis of Baseline Data from the PROSPECT Study

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Purpose: Treatment patterns and patient characteristics are not well elucidated among Japanese patients with severe uncontrolled asthma who currently have various treatment options, including biologics. We analyzed baseline characteristics of patients who did/did not initiate biologic treatment in PROSPECT, a 24-month observational study.

Patients and Methods: Patients with severe uncontrolled asthma were prospectively enrolled at 34 sites in Japan from December 2019 to September 2021. The enrolled population was divided based on initiation/non-initiation of biologic treatment within 12 weeks after enrollment. Patient demographics, clinical characteristics, biomarker levels, and asthma-related treatment were assessed at enrollment.

Results: Of 289 patients meeting the enrollment criteria, 127 patients initiated biologic treatment (BIO group: omalizumab, n = 16; mepolizumab, n = 10; benralizumab, n = 41; and dupilumab, n = 60) and 162 patients did not (non-BIO group). The proportion of patients with ≥2 asthma exacerbations was higher in the BIO group than the non-BIO group (65.0% vs 47.5%). Patients receiving omalizumab had the highest frequency of allergic rhinitis (87.5% vs other BIOs: 40.0%–53.3%). Patients receiving benralizumab and dupilumab had the highest incidence of nasal polyps (benralizumab: 19.5%, dupilumab: 23.3%, other BIOs: 0.0%). The proportion of patients with blood eosinophils ≥300 cells/μL was higher with benralizumab (75.6%) than other BIOs (26.7%–42.9%).

Conclusion: This analysis of baseline data from the PROSPECT study is the first to clarify the characteristics of Japanese patients with severe uncontrolled asthma. BIOs were not necessarily prescribed to patients in whom they were indicated; however, for patients who received them, selection appeared to be made appropriately based on asthma phenotypes.

Keywords: benralizumab, biologics, dupilumab, mepolizumab, omalizumab

Introduction

Asthma is a heterogeneous chronic inflammatory disease of the airways characterized by airway constriction and airway hyper-responsiveness with wheezing, cough, and exacerbations.[1] Severe asthma is defined as that requiring high-dose inhaled corticosteroids (ICS) and additional treatment.[1] Among patients with asthma in Japan, the prevalence of severe asthma is reported to range between 2.4% and 12.7%.[2–4] Patients with severe asthma have a higher risk of asthma exacerbations and progressive lung function decline compared with patients with non-severe asthma.[5] Systemic corticosteroids often prescribed to patients with severe asthma can lead to steroid-related comorbidities.[6] Furthermore, accelerated loss of lung function over time indicates asthma progression,[7,8] and it is partially driven by exacerbations.[9] Therefore, appropriate treatment, including biologics (BIOs), for patients with severe asthma is required.

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Currently, four BIOs (omalizumab, mepolizumab, benralizumab, and dupilumab) are approved and indicated for patients with severe asthma in Japan. In clinical trials, BIO treatment for patients with severe asthma is reported to decrease asthma exacerbations, improve quality of life and lung function,[10–16] and reduce the necessary dose of oral corticosteroids (OCS).[17–19] BIO use is recommended for patients with severe uncontrolled asthma treated with high-dose ICS/long-acting β_2-adrenoceptor agonists (LABA) and additional asthma treatment.[1] However, because of the high costs of BIOs, these drugs are not prescribed for severe asthma, even when they are indicated. In addition, it can be challenging to select an appropriate BIO for each patient with severe asthma based on the individual's biomarker profile, as the same patient may have multiple biomarkers, such as high eosinophils, high fractional exhaled nitric oxide (FeNO), and high immunoglobulin E (IgE), which suggest that the patient may be a candidate for targeted therapy with several of the BIOs available.[1] A better understanding of the treatment reality and characteristics of patients with severe uncontrolled asthma would be beneficial in improving treatment regimens and outcomes for patients. Several studies on cohorts of patients with severe asthma have been reported,[20,21] but the treatment patterns and patient characteristics of severe uncontrolled asthma in the real world have not yet been evaluated in a large cohort study since the four BIO options became available. Furthermore, to fully understand the reality of BIO use and selection, it is important to investigate these factors in a large severe asthma cohort to clarify the treatment reality for severe asthma in the real world.

PROSPECT is an observational study to compare the lung function between adult patients with severe asthma who initiated BIO treatment with those who did not initiate BIO treatment within 12 weeks of enrollment. The study's primary objective is to compare the change from baseline in post-bronchodilator forced expiratory volume in 1 second (FEV_1) at 24 months between patients who do/do not initiate treatment with BIOs after adjusting for differences in patient characteristics between groups. As secondary objectives, we aim to clarify the clinical characteristics, symptoms, exacerbations, and treatment patterns of both groups, and the baseline characteristics of patients according to the BIO therapy received. Here, we present the baseline characteristics of patients enrolled in this ongoing study.

Methods

Study Design

This multicenter, observational, 24-month, prospective cohort study is being conducted at 34 sites in Japan (a full list is provided in the Supplementary Methods). The enrollment period was from December 2019 to September 2021. Patients were enrolled consecutively, and registration, including eligibility verification, was managed at a single registration office. Patients are followed for 24 months after enrollment. The selected study sites were medical institutions (mainly large hospitals and university hospitals) with respiratory specialists and/or allergy specialists, who conducted follow-up per usual care.

This study is being conducted in accordance with the Declaration of Helsinki and all applicable national and international ethical guidelines for medical and health research involving human participants. All study documentation was approved by the NPO-MINS Institutional Review Board (22-August-2019; reference: 190228). All participants gave written informed consent before registration. Medical data were collected and stored in compliance with the relevant laws/regulations concerning data protection and the Personal Information Protection Act. This study was registered at the University Hospital Medical Information Network (UMIN000038006).

Patients

The enrolled population consisted of patients with asthma receiving high-dose ICS and additional asthma maintenance treatment for ≥3 months before registration and who were diagnosed with uncontrolled asthma based on the guidelines of the European Respiratory Society and American Thoracic Society.[22] Patients had to meet one or more of the following criteria: poor symptom control characterized by an Asthma Control Questionnaire (ACQ) score ≥1.5 or an Asthma Control Test score <20; frequent exacerbations (at least two asthma exacerbations within 12 months prior to registration); and/or airflow obstruction defined as a pre-bronchodilator FEV_1 <80% of predicted normal. Patients were also required to confirm their anticipated ability to visit the study site regularly during the following 24 months. Subsequently, each patient was evaluated to determine the need for treatment with BIOs, which was then explained to the patients by the

investigators. Patients with BIO use within 5 months before the study enrollment were excluded. The full eligibility criteria are provided in the Supplementary Methods. To avoid selection bias, investigators provided a full explanation of the study to all eligible patients prior to registration. All patients met the criteria for poorly controlled asthma and were thus suitable candidates for BIOs; however, the enrolled population was divided into two groups based on whether the patients decided to initiate or not initiate BIO treatment within 12 weeks after enrollment. These were designated as the BIO group and non-BIO group, respectively; the physician and patient agreed upon the treatment decision and selection based on the physician's routine clinical practice.

Study Assessment During the Registration Period

Patient demographics and clinical characteristics, biomarker levels, lung function, and asthma-related treatments were assessed at the time of enrollment. T2 high patients were defined as those having blood eosinophils ≥150 cells/μL, FeNO ≥25 ppb, or being omalizumab-eligible (total IgE 30–1500 IU/mL and perennial antigen-positive). T2 low patients were defined as those having blood eosinophils <150 cells/μL, FeNO <25 ppb, and being omalizumab non-eligible. At 12 weeks after registration, the type of BIO used and reasons why BIOs were not initiated were evaluated. Baseline patient background and clinical characteristics were described for all enrolled patients in the BIO and non-BIO groups, and by type of BIO received.

Statistical Analysis

The enrolled population was used as the analysis set for this baseline analysis. All data were summarized using descriptive statistics. The number and percentage of patients in each category were calculated for categorical variables. Continuous variables were reported using frequency, mean, standard deviation (SD), median, maximum, minimum, and interquartile range (IQR). For the baseline analysis, all statistical tests were conducted in an exploratory manner, and there were no adjustments for multiplicity and no imputation for missing or incomplete data. For comparison of categorical variables, a chi-square test was used in cases where the expected count per cell was ≥5 in 80% of the cells; otherwise, Fisher's exact test was used. For quantitative variables, the Levene test for equality of variances was performed. A one-way analysis of variance (ANOVA) was conducted if the variances were assumed to be equal; otherwise, a Welch's ANOVA was performed. All statistical analyses were performed using SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

Patient Demographic and Clinical Characteristics

A total of 306 patients with severe uncontrolled asthma were enrolled in the PROSPECT study from December 2019 to September 2021 at 34 sites in Japan. After excluding 17 patients who did not satisfy the eligibility criteria, 289 were identified as the enrollment population (Figure 1). Among the enrollment population, 127 patients initiated BIOs and 162 patients did not initiate BIOs within 12 weeks after enrollment. In the BIO group, 16 patients received omalizumab; 10 patients, mepolizumab; 41 patients, benralizumab; and 60 patients, dupilumab. The demographic and clinical characteristics of patients at enrollment are shown in Table 1. The mean (SD) age at enrollment was 59.7 (13.9) years, and the proportion of women was 61.2%. Lung function tests indicated that patients had significant airflow obstruction overall, with a mean (SD) post-bronchodilator FEV_1 77.8% (22.2%) of predicted normal. The proportion of patients treated with asthma-related medications was 85.5% for ICS/LABA, 77.9% for leukotriene receptor antagonists (LTRA), and 46.7% for long-acting muscarinic antagonists (LAMA). During the 12 months prior to enrollment, maintenance OCS was used by 28.4% of patients. Overall, patients had severe uncontrolled asthma with a mean (SD) ACQ-5 score of 1.95 (1.16), 13.0% had one exacerbation, and 55.1% had ≥2 exacerbations during the 12 months prior to enrollment. A breakdown of how patients in the enrollment population met one or more of the three criteria for uncontrolled asthma (airflow obstruction, poor symptom control, frequent exacerbations) is illustrated in Figure 2A.

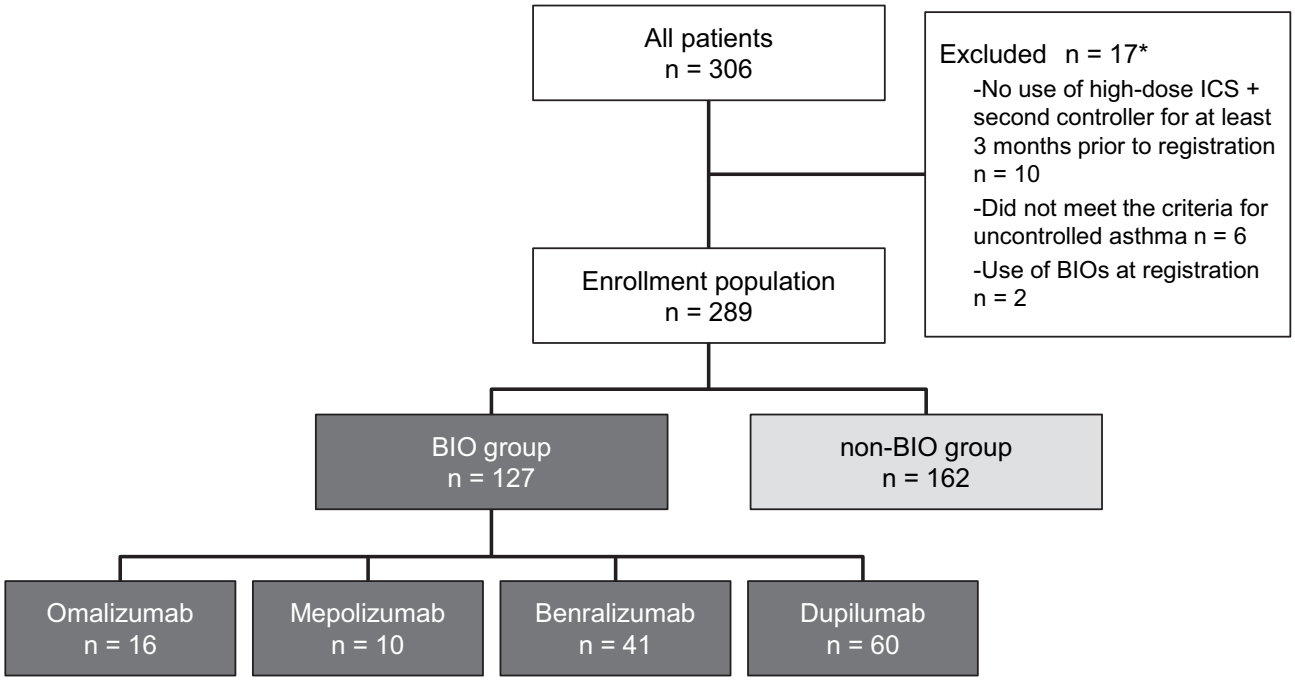

Figure 1 Patient disposition. *Patients may have been excluded for more than one reason.
Abbreviations: BIO, biologic; ICS, inhaled corticosteroids.

Differences in Patient Characteristics Between the BIO and Non-BIO Groups

An analysis of the differences in demographic and clinical characteristics between the BIO and non-BIO groups showed numerical differences in several domains (Table 1). Proportions of patients in the BIO group aged ≥65 years were 46.5%, and in the non-BIO group, 35.8%. In asthma-related comorbidities, the BIO group had more prevalent nasal polyps than the non-BIO group (17.3% and 6.8%, respectively).

Median (IQR) FeNO (36 [20–71] ppb and 26 [15–50] ppb) and median (IQR) neutrophil count (4851 [3224–5859] cells/μL and 3771 [2909–5314] cells/μL) were higher in the BIO group than the non-BIO group. In contrast, median (IQR) blood eosinophil count (304 [122–673] cells/μL and 248 [105–616] cells/μL) and median (IQR) total IgE (292 [96–620] IU/mL and 300 [82–705] IU/mL) were similar between groups.

Regarding asthma control status, the mean (SD) ACQ-5 score was higher in the BIO group than the non-BIO group (2.34 [1.17] and 1.64 [1.07], respectively), as was the proportion of patients with ≥2 asthma exacerbations (65.0% and 47.5%, respectively). In asthma treatment, maintenance OCS use 12 months before enrollment was higher in the BIO group than the non-BIO group (33.9% and 24.1%, respectively). Patients in the BIO group were more likely to meet all three criteria for uncontrolled asthma than those in the non-BIO group (26.8% vs 6.8%, respectively; Figure 2B and C). Approximately half of the patients in the non-BIO group met only one criterion for uncontrolled asthma, whereas the majority of patients in the BIO group met multiple criteria.

In the non-BIO group, the type 2 biomarkers evaluated were blood eosinophil count: 150 cells/μL, FeNO: 25 ppb, omalizumab-eligible: total IgE amount 30–1500 IU/mL, and positive for perennial antigen-specific IgE. Among 50 patients who had enough data to evaluate type 2 inflammation, only six patients (12.0%) had type 2 low inflammation.

Reasons BIOs Were Not Initiated

Despite investigators recommending that enrolled patients initiate BIOs in this study, 162 patients did not initiate BIO treatment within 12 weeks after enrollment. Among the reasons mentioned for not initiating BIOs, patients' refusal due to treatment costs was the most frequent answer (54.9%); 29.6% of patients refused to start BIOs for reasons other than cost, whereas 15.4% did not initiate treatment for reasons other than patient refusal (Figure 3). Among the other reasons, improvement of asthma symptoms, low T2 markers, advanced age, and postponement of BIO initiation were the most common.

Table 1 Patient Background and Clinical Characteristics at Baseline

Characteristics	Overall (N = 289)	BIO (N = 127)	Non-BIO (N = 162)	p-value
Age				
Mean (SD), years	59.7 (13.9)	60.4 (14.5)	59.1 (13.4)	0.442
<65 years, n (%)	172 (59.5)	68 (53.5)	104 (64.2)	0.067[a]
≥65 years, n (%)	117 (40.5)	59 (46.5)	58 (35.8)	
Female, n (%)	177 (61.2)	73 (57.5)	104 (64.2)	0.245[a]
BMI, mean (SD), kg/m^2	25.1 (4.6)	24.9 (4.3)	25.3 (4.8)	0.538
Smoking status, n (%)				
Current	13 (4.5)	3 (2.4)	10 (6.2)	0.200[b]
Former	115 (39.8)	48 (37.8)	67 (41.4)	
Never	161 (55.7)	76 (59.8)	85 (52.5)	
Smoking history, mean (SD), pack-years	23.9 (25.3)	22.8 (28.9)	24.7 (22.7)	0.686
Duration of asthma, mean (SD), years	20.0 (15.2)	21.5 (16.9)	18.9 (13.6)	0.167
History of pediatric asthma, n (%)				
Yes	64 (22.1)	36 (28.3)	28 (17.3)	0.056[a]
No	207 (71.6)	82 (64.6)	125 (77.2)	
Unknown	18 (6.2)	9 (7.1)	9 (5.6)	
Family history of asthma, n (%)	79 (27.3)	35 (27.6)	44 (27.2)	0.775[a]
Comorbidities, n (%)				
Allergic rhinitis				
Yes	168 (58.1)	71 (55.9)	97 (59.9)	0.466[a]
No	120 (41.5)	55 (43.3)	65 (40.1)	
Unknown	1 (0.4)	1 (0.8)	0	
Nasal polyp				
Yes	33 (11.4)	22 (17.3)	11 (6.8)	0.015[a]
No	250 (86.5)	102 (80.3)	148 (91.4)	
Unknown	6 (2.1)	3 (2.4)	3 (1.9)	
Atopic dermatitis				
Yes	25 (8.7)	12 (9.4)	13 (8.0)	0.669[a]
No	264 (91.3)	115 (90.6)	149 (92.0)	
Urticaria				
Yes	31 (10.7)	12 (9.4)	19 (11.7)	0.444[a]
No	257 (88.9)	114 (89.8)	143 (88.3)	
Unknown	1 (0.3)	1 (0.8)	0	
Post-BD[c] FEV_1	n = 273	n = 120	n = 153	
Mean (SD), L	1.97 (0.77)	2.00 (0.85)	1.95 (0.70)	0.609
Post-BD FEV_1 predicted normal	n = 273	n = 120	n = 153	
Mean (SD), %	77.8 (22.2)	77.4 (22.3)	78.2 (22.2)	0.757
Post-BD FEV_1/FVC	n = 273	n = 120	n = 153	
Mean (SD), %	69.0 (14.7)	68.8 (13.8)	69.2 (15.5)	0.818
Medical treatment, n (%)				
ICS	32 (11.1)	16 (12.6)	16 (9.9)	0.464[a]
ICS/LABA	247 (85.5)	102 (80.3)	145 (89.5)	0.028[a]
ICS/LABA/LAMA	30 (10.4)	19 (15.0)	11 (6.8)	0.024[a]
LTRA	225 (77.9)	101 (79.5)	124 (76.5)	0.544[a]
LAMA	135 (46.7)	50 (39.4)	85 (52.5)	0.027[a]
Theophylline	96 (33.2)	41 (32.3)	55 (34.0)	0.765[a]
OCS	58 (20.1)	34 (26.8)	24 (14.8)	0.012[a]
Maintenance-use OCS 12 months before enrollment, n (%)				
Yes	82 (28.4)	43 (33.9)	39 (24.1)	0.036[a]
No	205 (70.9)	82 (64.6)	123 (75.9)	
Unknown	2 (0.7)	2 (1.6)	0	

(*Continued*)

Table 1 (Continued).

Characteristics	Overall (N = 289)	BIO (N = 127)	Non-BIO (N = 162)	p-value
FeNO	n = 236	n = 109	n = 127	
Mean (SD), ppb	49.0 (50.9)	57.3 (56.8)	41.9 (44.2)	0.021
Median (IQR), ppb	31 (18–64)	36 (20–71)	26 (15–50)	
<25 ppb, n (%)	91 (38.6)	33 (30.3)	58 (45.7)	0.015[a]
≥25 ppb, n (%)	145 (61.4)	76 (69.7)	69 (54.3)	
Blood eosinophil count	n = 235	n = 117	n = 118	
Mean (SD), cells/μL	438 (432)	468 (451)	408 (413)	0.296
Median (IQR), cells/μL	282 (107–639)	304 (122–673)	248 (105–616)	
<150 cells/μL, n (%)	75 (31.9)	33 (28.2)	42 (35.6)	0.465[a]
150–300 cells/μL, n (%)	47 (20.0)	24 (20.5)	23 (19.5)	
≥300 cells/μL, n (%)	113 (48.1)	60 (51.3)	53 (44.9)	
Blood neutrophil count	n = 235	n = 117	n = 118	
Mean (SD), cells/μL	4632 (2219)	4972 (2354)	4295 (2032)	0.019
Median (IQR), cells/μL	4352 (3004–5636)	4851 (3224–5859)	3771 (2909–5314)	
Total IgE	n = 196	n = 102	n = 94	
Mean (SD), IU/mL	819 (1906)	927 (2372)	702 (1216)	0.411
Median (IQR), IU/mL	299 (88–681)	292 (96–620)	300 (82–705)	
<30 IU/mL, n (%)	22 (11.2)	13 (12.7)	9 (9.6)	0.681[a]
30–1500 IU/mL, n (%)	149 (76.0)	75 (73.5)	74 (78.7)	
≥1500 IU/mL, n (%)	25 (12.8)	14 (13.7)	11 (11.7)	
Allergen test for perennial antigen	n = 161	n = 88	n = 73	
Positive, n (%)	117 (72.7)	62 (70.5)	55 (75.3)	0.488[a]
Negative, n (%)	44 (27.3)	26 (29.5)	18 (24.7)	
ACQ-5 score	n = 285	n = 124	n = 161	
Mean (SD)	1.95 (1.16)	2.34 (1.17)	1.64 (1.07)	<0.001[b]
Number of asthma exacerbations 12 months before enrollment	n = 285	n = 123	n = 162	
Mean (SD)	2.6 (3.8)	3.3 (4.7)	2.1 (2.8)	0.013
0, n (%)	91 (31.9)	33 (26.8)	58 (35.8)	0.008[a]
1, n (%)	37 (13.0)	10 (8.1)	27 (16.7)	
≥2, n (%)	157 (55.1)	80 (65.0)	77 (47.5)	
Number of ER visits in prior 12 months	n = 289	n = 127	n = 162	
Mean (SD)	0.41 (1.47)	0.50 (1.88)	0.33 (1.05)	0.329
Number of hospitalizations 12 months before enrollment	n = 289	n = 127	n = 162	
Mean (SD)	0.11 (0.50)	0.17 (0.67)	0.07 (0.30)	0.074
Type 2 signatures[d]			n = 50	
T2-low[e], n (%)	-	-	6 (12.0)	-
T2-high[f], n (%)	-	-	44 (88.0)	-

Notes: [a]A chi-square test was performed to calculate the probability if the value was 5 or higher in 80% of the cells. If the assumption was not met, Fisher's exact test was used. [b]A one-way ANOVA alongside the Levene test for the equality of variances was performed. If the variances could not be assumed as equal, Welch's ANOVA was calculated instead. [c]Post-BD: Patients could use a bronchodilator in the morning of the test day as a usual daily medication. Because this was an observational rather than an interventional study, BD use as usual medication was not prohibited. [d]Type 2 signatures were analyzed in patients with complete data for eosinophil count, FeNO, total IgE, and allergen test for perennial antigen. [e]Blood eosinophil <150 cells/μL, FeNO <25 ppb, and omalizumab non-eligible. [f]Blood eosinophil ≥150 cells/μL, FeNO ≥25 ppb, or omalizumab-eligible (total IgE 30–1500 IU/mL and perennial antigen-positive).

Abbreviations: ACQ, Asthma Control Questionnaire; ANOVA, analysis of variance; BD, bronchodilator; BIO, biologic; BMI, body mass index; ER, emergency room; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IQR, interquartile range; LABA, long-acting β_2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SD, standard deviation.

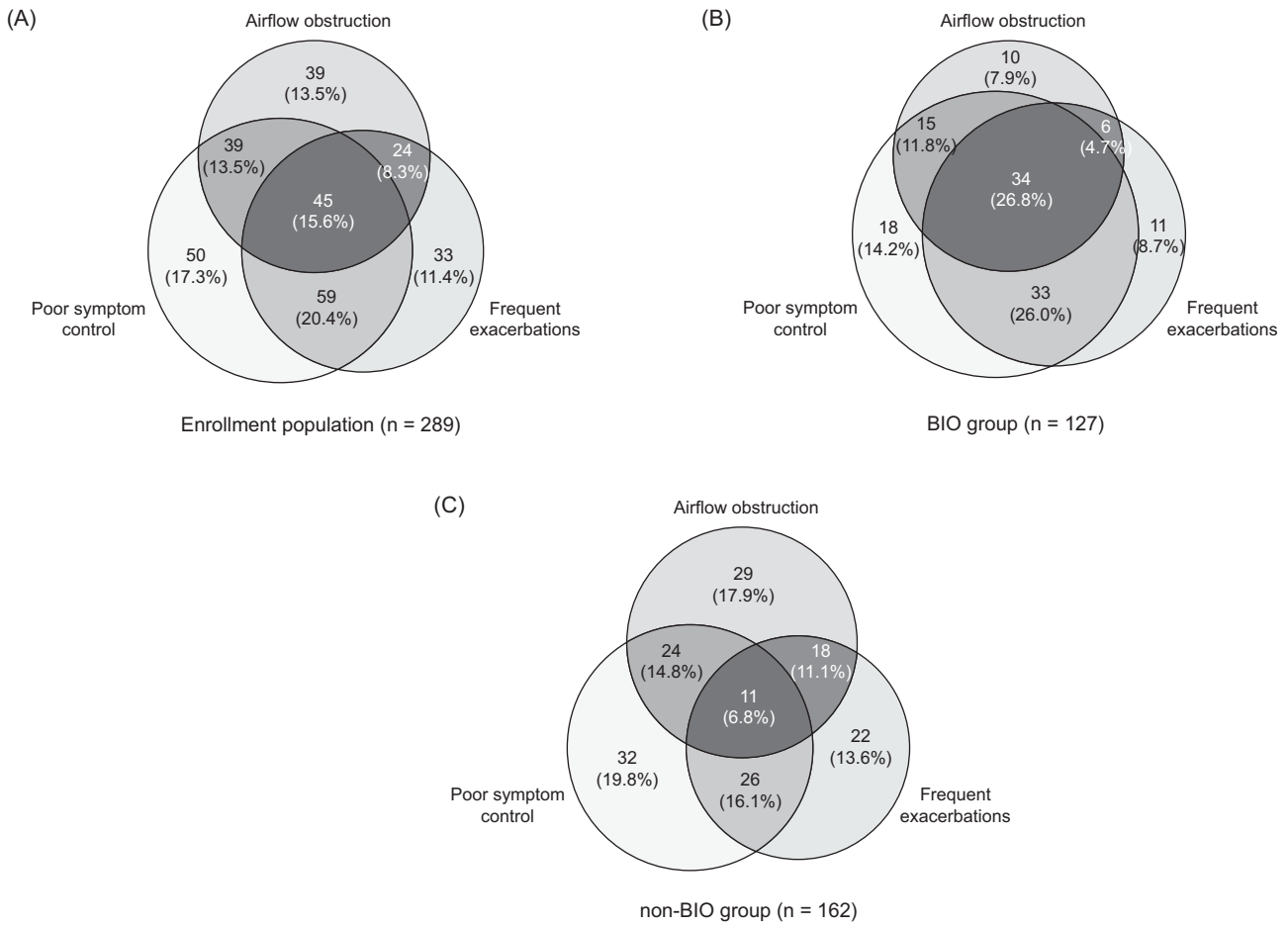

Figure 2 Venn diagrams illustrating how patients met the criteria for uncontrolled asthma in the (**A**) enrollment population, (**B**) BIO group, and (**C**) non-BIO group. Poor symptom control: ACQ-5 ≥1.5 or ACT <20. Frequent exacerbations: at least two asthma exacerbations within 12 months prior to registration. Airflow obstruction: post-bronchodilator FEV_1 <80% of predicted normal. Patients with missing data or unknown in each criterion have been categorized as "not met".
Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; BIO, biologic; FEV_1, forced expiratory volume in 1 second.

Differences in Clinical Characteristics of Patients by BIO Received (Omalizumab, Mepolizumab, Benralizumab, and Dupilumab)

An analysis of the demographic and clinical characteristics of patients who initiated each BIO (omalizumab n = 16, mepolizumab n = 10, benralizumab n = 41, and dupilumab n = 60) highlighted numerical differences in several domains (Table 2). At registration, patients receiving omalizumab were younger (mean [SD]: 52.8 [19.4] years) than those receiving dupilumab (59.0 [12.8] years) and those receiving other BIOs (63.8–64.5 years). A history of pediatric asthma was more common among those receiving omalizumab (56.3%) than other BIOs (17.1%–30.0%). Regarding comorbidities related to BIO indication, allergic rhinitis was more frequent among patients receiving omalizumab (87.5%) than those receiving other BIOs (40.0%–53.3%). Nasal polyps were more frequent among patients receiving benralizumab (19.5%) and dupilumab (23.3%) than those receiving other BIOs (0.0%).

Relevant differences were noted by type of BIO. Higher blood eosinophil counts ($p<0.001$) were observed among patients receiving benralizumab than those receiving other BIOs. The proportion of patients with blood eosinophil count ≥300 cells/μL was higher in patients receiving benralizumab (75.6%) than other BIOs (26.7%–42.9%).

Regarding type 2 biomarkers, the proportion of patients with ≥25 ppb FeNO was higher among benralizumab-treated patients (78.4%) and dupilumab-treated patients (75.5%) than patients receiving other BIOs (30.8%–50.0%). Total IgE and allergen test results for perennial antigen, which are related to omalizumab eligibility, were polarized: total IgE (30–1500 IU/mL) omalizumab, 100%; others, 50.0%–70.6%; positive for perennial antigen-specific IgE: omalizumab, 100%; others, 65.3%–66.7%.

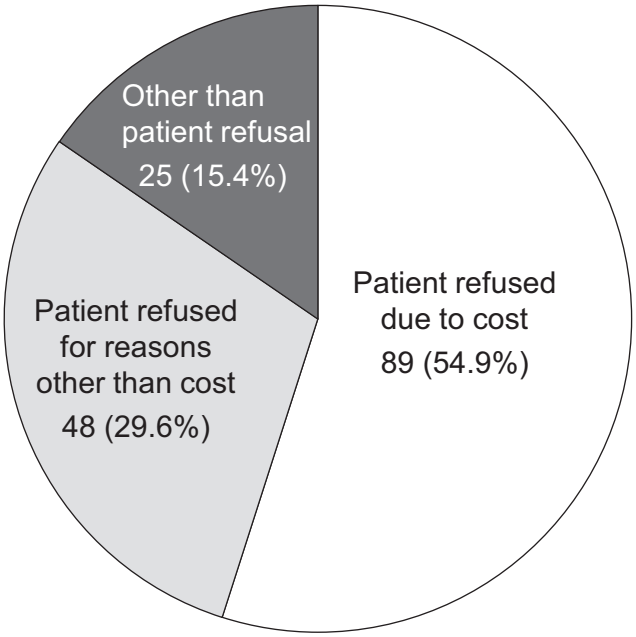

Figure 3 Reason biologics were not initiated within 12 weeks of enrollment in the non-BIO group.
Abbreviation: BIO, biologic.

The proportion of patients with asthma exacerbations within 12 months prior to enrollment was higher among those who initiated treatment with benralizumab (≥2 asthma exacerbations, 78.9%) compared with those initiating treatment with other BIOs (50.0%–60.0%). A higher proportion of patients receiving mepolizumab (50.0%) and dupilumab (36.7%) had no exacerbations within 12 months of enrollment compared with 13.2% of those receiving benralizumab, and 6.7% of those receiving omalizumab (p = 0.001). Post-bronchodilator FEV_1 was lower in patients initiating benralizumab (1.74 L) and higher in patients initiating omalizumab (2.33 L) than other BIOs (2.02–2.09 L).

Table 2 Demographic and Clinical Characteristics at Baseline of Patients in the BIO Group (N = 127) by Type of BIO Received

Characteristics	Omalizumab (N = 16)	Mepolizumab (N = 10)	Benralizumab (N = 41)	Dupilumab (N = 60)	p-value
Age					
Mean (SD), years	52.8 (19.4)	63.8 (16.7)	64.5 (13.2)	59.0 (12.8)	0.090
<65 years, n (%)	9 (56.3)	4 (40.0)	18 (43.9)	37 (61.7)	0.272[a]
≥65 years, n (%)	7 (43.8)	6 (60.0)	23 (56.1)	23 (38.3)	
History of pediatric asthma, n (%)					
Yes	9 (56.3)	2 (20.0)	7 (17.1)	18 (30.0)	0.101[a]
No	6 (37.5)	7 (70.0)	30 (73.2)	39 (65.0)	
Unknown	1 (6.3)	1 (10.0)	4 (9.8)	3 (5.0)	
Comorbidities, n (%)					
Allergic rhinitis					
Yes	14 (87.5)	4 (40.0)	21 (51.2)	32 (53.3)	0.048[a]
No	2 (12.5)	6 (60.0)	19 (46.3)	28 (46.7)	
Unknown	0	0	1 (2.4)	0	
Nasal polyp					
Yes	0	0	8 (19.5)	14 (23.3)	0.057[a]
No	16 (100)	9 (90.0)	33 (80.5)	44 (73.3)	
Unknown	0	1 (10.0)	0	2 (3.3)	
Atopic dermatitis					
Yes	2 (12.5)	0	2 (4.9)	8 (13.3)	0.383[a]
No	14 (87.5)	10 (100)	39 (95.1)	52 (86.7)	

(*Continued*)

Table 2 (Continued).

Characteristics	Omalizumab (N = 16)	Mepolizumab (N = 10)	Benralizumab (N = 41)	Dupilumab (N = 60)	p-value
Urticaria					
Yes	1 (6.3)	1 (10.0)	4 (9.8)	6 (10.0)	0.885[a]
No	15 (93.8)	9 (90.0)	36 (87.8)	54 (90.0)	
Unknown	0	0	1 (2.4)	0	
Post-BD[b] FEV_1, L	n = 15	n = 9	n = 40	n = 56	
Mean (SD)	2.33 (1.12)	2.02 (1.44)	1.74 (0.63)	2.09 (0.75)	0.070
Medical treatment, n (%)					
ICS	5 (31.3)	0	6 (14.6)	5 (8.3)	0.072[a]
ICS/LABA	10 (62.5)	7 (70.0)	36 (87.8)	49 (81.7)	0.138[a]
ICS/LABA/LAMA	5 (31.3)	3 (30.0)	3 (7.3)	8 (13.3)	0.056[a]
LTRA	11 (68.8)	8 (80.0)	33 (80.5)	49 (81.7)	0.685[a]
LAMA	5 (31.3)	5 (50.0)	17 (41.5)	23 (38.3)	0.792[a]
Theophylline	7 (43.8)	5 (50.0)	16 (39.0)	13 (21.7)	0.086[a]
OCS	5 (31.3)	3 (30.0)	11 (26.8)	15 (25.0)	0.934[a]
Maintenance use of OCS 12 months before the study, n (%)					
Yes	8 (50.0)	3 (30.0)	14 (34.1)	18 (30.0)	0.784[a]
No	8 (50.0)	7 (70.0)	26 (63.4)	41 (68.3)	
Unknown	0	0	1 (2.4)	1 (1.7)	
FeNO	n = 13	n = 6	n = 37	n = 53	
Mean (SD), ppb	24.9 (20.8)	32.8 (29.7)	67.0 (58.4)	61.2 (61.2)	0.081
Median (IQR), ppb	16 (12–26)	26 (18–33)	50 (27–75)	36 (25–74)	
<25 ppb, n (%)	9 (69.2)	3 (50.0)	8 (21.6)	13 (24.5)	0.006[a]
≥25 ppb, n (%)	4 (30.8)	3 (50.0)	29 (78.4)	40 (75.5)	
Blood eosinophil count	n = 15	n = 7	n = 41	n = 54	
Mean (SD), cells/μL	233 (280)	395 (449)	683 (525)	379 (365)	<0.001
Median (IQR), cells/μL	122 (43–328)	86 (30–750)	508 (301–970)	269 (104–540)	
<150 cells/μL, n (%)	9 (60.0)	4 (57.1)	3 (7.3)	17 (31.5)	<0.001[a]
150–300 cells/μL, n (%)	2 (13.3)	0	7 (17.1)	15 (27.8)	
≥300 cells/μL, n (%)	4 (26.7)	3 (42.9)	31 (75.6)	22 (40.7)	
Blood neutrophil count, cells/μL	n = 15	n = 7	n = 41	n = 54	
Mean (SD)	5489 (2855)	5148 (1247)	4845 (2313)	4902 (2379)	0.822
Median (IQR)	4398 (3123, 8595)	5532 (4627, 5859)	4828 (3000, 6147)	4675 (3314, 5467)	
Total IgE	n = 14	n = 4	n = 33	n = 51	
Mean (SD), IU/mL	353 (353)	96 (157)	1095 (2110)	1041 (2882)	0.668
Median (IQR), IU/mL	155 (120–598)	24 (12–181)	310 (180–956)	300 (86–674)	
<30 IU/mL, n (%)	0	2 (50.0)	3 (9.1)	8 (15.7)	0.078[a]
30–1500 IU/mL, n (%)	14 (100)	2 (50.0)	23 (69.7)	36 (70.6)	
≥1500 IU/mL, n (%)	0	0	7 (21.2)	7 (13.7)	
Allergen test for perennial antigen	n = 12	n = 6	n = 21	n = 49	
Positive, n (%)	12 (100)	4 (66.7)	14 (66.7)	32 (65.3)	0.068[a]
Negative, n (%)	0	2 (33.3)	7 (33.3)	17 (34.7)	
ACQ-5 score	n = 16	n = 9	n = 39	n = 60	
Mean (SD)	2.45 (1.36)	2.87 (1.02)	2.39 (1.18)	2.20 (1.14)	0.409[c]
Number of asthma exacerbations in prior 12 months	n = 15	n = 10	n = 38	n = 60	
Mean (SD)	4.5 (6.1)	5.3 (8.2)	3.7 (5.3)	2.4 (2.5)	0.152
0, n (%)	1 (6.7)	5 (50.0)	5 (13.2)	22 (36.7)	0.001[a]
1, n (%)	5 (33.3)	0	3 (7.9)	2 (3.3)	
≥2, n (%)	9 (60.0)	5 (50.0)	30 (78.9)	36 (60.0)	

Notes: [a]A chi-square test was performed to calculate the probability if the value was 5 or higher in 80% of the cells. If the assumption was not met, Fisher's exact test was used. [b]Post-BD: Patients could use a bronchodilator in the morning of the test day as a usual daily medication. Because this was an observational rather than an interventional study, BD use as usual medication was not prohibited. [c]A one-way ANOVA alongside the Levene test for the equality of variances was performed. If the variances could not be assumed as equal, Welch's ANOVA was calculated instead.

Abbreviations: ACQ, Asthma Control Questionnaire; ANOVA, analysis of variance; BD, bronchodilator; BIO, biologic; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; IgE, immunoglobulin E; IQR, interquartile range; LABA, long-acting β_2-adrenoceptor agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; SD, standard deviation.

Discussion

This baseline analysis of the PROSPECT study is the first to evaluate patient demographic and clinical characteristics and treatment patterns of patients with severe uncontrolled asthma in the clinical setting in Japan, where there are four BIO treatment options available. We observed that patients receiving BIOs had higher FeNO, higher prevalence of comorbidities, including nasal polyps, and a higher rate of uncontrolled asthma status (based on ACQ-5 score and asthma exacerbations in the past year) compared with the non-BIO group. Despite all enrolled patients being eligible for BIOs, those meeting multiple criteria for uncontrolled asthma[22] were more likely to be prescribed a BIO compared with patients meeting only a single criterion. Patients receiving benralizumab and those receiving dupilumab had eosinophilic phenotype-related features, including higher eosinophil counts, higher FeNO value, and comorbidities like nasal polyps. Patients receiving omalizumab had allergy-related features, including a history of pediatric asthma and allergic rhinitis. Thus, the present results showed that each BIO was selected for patients with severe uncontrolled asthma based on their asthma phenotype.

Regarding patient background characteristics, we found that important factors in determining asthma phenotype, such as sex, smoking history, and childhood asthma status, were similar in the PROSPECT cohort compared with those of other studies of patients with severe asthma in Japan.[23,24] This suggests that the PROSPECT population is likely to be representative of the Japanese severe asthma population. Moreover, we were able to recruit more patients in the present study than the abovementioned studies, further strengthening our results.

Compared with the non-BIO group, the BIO group included more elderly patients (aged ≥65 years). This difference could be attributed to the difference in self-payment costs. In the Japanese health insurance system, self-payment costs are lower for older patients. Generally, patients under age 70 are responsible for 30% of their total medical expenses, whereas the self-pay rate drops to 20% for patients aged 70–74 years and 10% for patients aged ≥75 years.[25] Among comorbidities related to the indication of BIOs, the prevalence of nasal polyps with high FeNO (ie, eosinophilic sinusitis) was higher in the BIO group than in the non-BIO group. The Japanese government designated eosinophilic sinusitis as an intractable disease to ensure better management and support for these patients; such patients are eligible for additional financial support for their treatment, including expensive medications such as BIOs. Conversely, the proportions of other comorbidities related to BIO indications, including allergic rhinitis, atopic dermatitis, and urticaria, which are not designated intractable diseases, were similar between the BIO and non-BIO groups, suggesting that the self-payment costs of medication may have affected the patients' decision to initiate BIOs. Moreover, the BIO group had asthma exacerbations more frequently and higher proportions of patients using maintenance OCS. Strengthening asthma treatment with BIOs was recommended for reducing asthma exacerbations and the use of maintenance OCS in these patients. Therefore, the decision to initiate BIO treatment in patients with severe asthma was affected not only by the physicians' recommendations, but also by the patients' ability to afford the medication, the extent of exacerbations, and OCS use.

Of note, there were no differences in the eosinophil count and IgE, but there was a difference in neutrophil count between the BIO and non-BIO groups. This was probably because of the difference in OCS use between the groups, as OCS are known to increase blood neutrophil count.[26] In the non-BIO group, 47.5% of patients had ≥2 asthma exacerbations. Moreover, in this group, of 50 patients with type 2 biomarker data, 88.0% had one or more type 2 inflammation features, including high eosinophil count, high FeNO, high total IgE, and presence of perennial antigen-specific IgE. The reasons BIOs were not initiated were patient refusal due to cost (54.9%), patient refusal other than cost (29.6%), and other reasons (15.4%). Other reasons included improvement of asthma symptoms, low T2 markers, advanced age, and postponement of BIO initiation. In the KOFU study,[27] similar results were reported. In that study, for patients who were recommended BIO treatment, the cost of treatment was reported as the reason for refusal in approximately half of the cases, which is in agreement with the results of our study, in which slightly over half of the patients refused BIOs because of the cost. These results should raise awareness that the cost of BIO treatment is a sizable barrier for patients to initiate needed therapy, and should support advocacy efforts to get better funding for such medications to treat severe asthma. Although cost was the primary reason for not initiating BIO treatment, there were also other reasons for refusal in this study. Moreover, in the KOFU study, other reasons for refusal of BIO initiation included satisfaction with current treatment, good symptom control according to patient perception, and a lack of

understanding of BIO treatment options, suggesting that it is important not only for the physicians but also other medical practitioners to adequately inform patients of newer treatment options. These results suggest that barriers to optimal treatment other than the cost of medication are common and should be addressed. Unfortunately, we did not collect further details on reasons for refusal other than cost; a future study would be useful to clarify all possible factors influencing a patient's decision not to undergo treatment with BIOs.

Our results also showed that BIOs were selected based on the phenotype of patients with severe asthma. Patients receiving benralizumab had higher eosinophil counts, higher FeNO, lower post-bronchodilator FEV_1, and a higher prevalence of nasal polyps. Patients receiving dupilumab had higher FeNO and a higher prevalence of nasal polyps. Additionally, patients receiving dupilumab had fewer exacerbations prior to enrollment. Accordingly, dupilumab might be useful for the treatment of concomitant diseases such as chronic sinusitis and atopic dermatitis. Conversely, age tended to be lower, and the proportion of patients with a history of pediatric asthma and allergic rhinitis tended to be higher among patients receiving omalizumab compared with other BIOs. These results suggest that omalizumab was selected for the early-onset allergic phenotype, and benralizumab and dupilumab were selected for the late-onset eosinophilic phenotype.[28] Patient characteristics differed according to the BIOs prescribed, and the current findings were similar to those described by Brusselle et al.[29] Overall, these findings suggest that the selection of BIOs in Japanese clinical practice is appropriate. These results are also consistent with characteristics of anti-IgE-treated patients and anti-IL-5-treated patients in the UK Severe Asthma Registry study.[30]

Regarding the differences between benralizumab and dupilumab, a higher proportion of benralizumab patients had asthma exacerbations, whereas 37% of patients receiving dupilumab had no asthma exacerbations. This implies that benralizumab was mainly prescribed to patients with a history of frequent exacerbations, and dupilumab was mainly prescribed to those with less frequent exacerbations and comorbidities, including chronic rhinosinusitis and nasal polyps.

Some limitations of this study should be noted. This study was conducted at 34 sites where respiratory specialists and/or allergy specialists mainly belonged to university hospitals and large hospitals. Most patients with severe asthma were treated in hospitals with allergy and respiratory specialists, which may affect the generalizability of the present results. We did not evaluate treatment adherence for asthma medications, although the investigators were specialists familiar with the Japanese guidelines, which stress the importance of monitoring treatment adherence.[31] In addition, clinical data from medical records might vary among facilities because of differing definitions of some of the evaluated variables/parameters. Finally, differences in patient numbers should be considered when interpreting the differences among the BIO treatment groups, especially for mepolizumab, which was prescribed to only 10 patients.

In conclusion, this analysis of the baseline data of the PROSPECT study is the first to clarify that BIOs were not necessarily initiated in patients in whom they were indicated. However, among those who did initiate treatment with BIOs, the selection appeared to be appropriately conducted based on asthma phenotypes.

Data Sharing Statement

Data underlying the findings described in this manuscript may be obtained in accordance with AstraZeneca's data sharing policy described at https://astrazenecagrouptrials.pharmacm.com/ST/Submission/Disclosure.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Nakamura Y, Tamaoki J, Nagase H, et al. Japanese guidelines for adult asthma 2020. *Allergol Int*. 2020;69:519–548. doi:10.1016/j.alit.2020.08.001
2. Nagase H, Adachi M, Matsunaga K, et al. Prevalence, disease burden, and treatment reality of patients with severe, uncontrolled asthma in Japan. *Allergol Int*. 2020;69:53–60. doi:10.1016/j.alit.2019.06.003
3. Sato K, Ohno T, Ishii T, Ito C, Kaise T. The prevalence, characteristics, and patient burden of severe asthma determined by using a Japan health care claims database. *Clin Ther*. 2019;41:2239–2251. doi:10.1016/j.clinthera.2019.08.015
4. Inoue H, Kozawa M, Milligan KL, Funakubo M, Igarashi A, Loefroth E. A retrospective cohort study evaluating healthcare resource utilization in patients with asthma in Japan. *NPJ Prim Care Respir Med*. 2019;29:13. doi:10.1038/s41533-019-0128-8
5. Calhoun WJ, Haselkorn T, Miller DP, Omachi TA. Asthma exacerbations and lung function in patients with severe or difficult-to-treat asthma. *J Allergy Clin Immunol*. 2015;136:1125–1127. doi:10.1016/j.jaci.2015.05.014
6. Matsunaga K, Adachi M, Nagase H, Okoba T, Hayashi N, Tohda Y. Association of low-dosage systemic corticosteroid use with disease burden in asthma. *NPJ Prim Care Respir Med*. 2020;30:35. doi:10.1038/s41533-020-00192-x
7. McGeachie MJ, Yates KP, Zhou X, et al. Patterns of growth and decline in lung function in persistent childhood asthma. *N Engl J Med*. 2016;374:1842–1852. doi:10.1056/NEJMoa1513737
8. Menzies-Gow A, Szefler SJ, Busse WW. The relationship of asthma biologics to remission for asthma. *J Allergy Clin Immunol Pract*. 2021;9:1090–1098. doi:10.1016/j.jaip.2020.10.035
9. O'Byrne P, Fabbri LM, Pavord ID, Papi A, Petruzzelli S, Lange P. Asthma progression and mortality: the role of inhaled corticosteroids. *Eur Respir J*. 2019;54:1900491. doi:10.1183/13993003.00491-2019
10. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β_2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2115–2127. doi:10.1016/S0140-6736(16)31324-1
11. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388:2128–2141. doi:10.1016/S0140-6736(16)31322-8
12. Haldar P, Brightling C, Hargadon B, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med*. 2009;360:973–984. doi:10.1056/NEJMoa0808991
13. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154:573–582. doi:10.7326/0003-4819-154-9-201105030-00002
14. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371:1198–1207. doi:10.1056/NEJMoa1403290
15. Pavord ID, Korn S, Howarth P, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet*. 2012;380:651–659. doi:10.1016/S0140-6736(12)60988-X
16. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β_2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388:31–44. doi:10.1016/S0140-6736(16)30307-5
17. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371:1189–1197. doi:10.1056/NEJMoa1403291

18. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376:2448–2458. doi:10.1056/NEJMoa1703501
19. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378:2475–2485. doi:10.1056/NEJMoa1804093
20. Matsusaka M, Fukunaga K, Kabata H, Izuhara K, Asano K, Betsuyaku T. Subphenotypes of type 2 severe asthma in adults. *J Allergy Clin Immunol Pract*. 2018;6:274–6.e2. doi:10.1016/j.jaip.2017.06.015
21. Kimura H, Makita H, Taniguchi N, et al. Determination of the cutoff values of Th2 markers for the prediction of future exacerbation in severe asthma: an analysis from the Hokkaido severe asthma cohort study. *Allergol Int*. 2021;70:68–73. doi:10.1016/j.alit.2020.09.001
22. Chung KF, Wenzel SE, Brozek JL, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J*. 2014;43:343–373. doi:10.1183/09031936.00202013
23. Tanosaki T, Kabata H, Matsusaka M, et al. 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. *Allergol Int*. 2021;70:61–67. doi:10.1016/j.alit.2020.06.002
24. Kimura H, Konno S, Nakamaru Y, et al. Sinus computed tomographic findings in adult smokers and nonsmokers with asthma. Analysis of clinical indices and biomarkers. *Ann Am Thorac Soc*. 2017;14:332–341. doi:10.1513/AnnalsATS.201606-463OC
25. Ministry of Health, Labour and Welfare, Japan. 高齢者医療制度 [Medical System for the Elderly]. Available from: https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/iryouhoken/koukikourei/index.html. Accessed September 30, 2022. Japanese.
26. Bjornson BH, Harvey JM, Rose L. Differential effect of hydrocortisone on eosinophil and neutrophil proliferation. *J Clin Invest*. 1985;76:924–929. doi:10.1172/JCI112091
27. Tamada T, Fukui K, Makita N, et al. 重症喘息患者における生物学的製剤の推奨プロセスに関するインターネット調査 (KOFU study 第2報) [An internet survey on the recommendation process of biologics in severe asthma patients]. *Ther Res*. 2021;42:857–866. Japanese.
28. Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med*. 2012;18:716–725. doi:10.1038/nm.2678
29. Brusselle GG, Koppelman GH. Biologic therapies for severe asthma. *N Engl J Med*. 2022;386:157–171. doi:10.1056/NEJMra2032506
30. Jackson DJ, Busby J, Pfeffer PE, et al. Characterisation of patients with severe asthma in the UK Severe Asthma Registry in the biologic era. *Thorax*. 2021;76:220–227. doi:10.1136/thoraxjnl-2020-215168
31. Horiguchi T, Kuwabara K, Kato R. 難治性喘息診断と治療の手引き2019 (成人) [The JRS guidelines 2019 for the management of refractory asthma]. *Arerugi*. 2021;70:10–14. Japanese. doi:10.15036/arerugi.70.10