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Original Article

Characteristics of the European Thoracic Society/American Thoracic Society severe asthma definition as a determinant of future use of biologics/bronchial thermoplasty

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ABSTRACT

Background: International guidelines define severe uncontrolled asthma. Biologics or bronchial thermoplasty (Bio/BT) are recommended for such patients.
Objectives: To determine which definitions of severe uncontrolled asthma are associated with an additional Bio/BT treatment in patients with severe uncontrolled asthma.
Methods: Consecutive 107 asthmatics (including 15 patients for whom Bio/BT was introduced within 3 months after examination), classified as treatment step 4 according to the Global Initiative for Asthma 2015 guideline, were eligible for this analysis. Patients were assessed using the European Thoracic Society/American Thoracic Society (ERS/ATS) severe uncontrolled asthma guideline as defined by these 4 characteristics: poor control (ACT < 20), frequent exacerbations (≥2/yr), admissions (≥1/yr), and airflow limitation (forced expiratory volume in 1 second < 80% of predicted), along with comorbidities, and biomarkers, including blood granulocytes, fractional nitric oxide, and capsaicin cough reflex sensitivity (C-CS). These indices were compared between patients with and without Bio/BT introduction, and multivariate logistic regression analysis was performed to determine the association of the 4 definitions with treatment needs for Bio/BT.
Results: Patients who were introduced to Bio/BT had heightened C-CS, heavier smoking history, and a greater prevalence of diabetes mellitus than those without ($p < 0.05$). Poor asthma control (ACT < 20), frequent exacerbations (≥2/yr), and admissions (≥1/yr) were relevant to the future use of Bio/BT in the multivariate regression analysis. Type 2-related biomarkers including absolute eosinophil counts were higher in patients in the Bio introduction group than in the BT introduction group. Meanwhile, there was no significant difference of the 4 characteristics of severe uncontrolled asthma definition between patients in the Bio and those in the BT groups.
Conclusion: Although multiple factors such as treatment cost and asthma phenotypes affect treatment decision-making, the definition of poor asthma control, frequent exacerbations and admission by the ERS/ATS guidelines were important factors for an additional intensive treatment for severe uncontrolled asthma.

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Conflict of Interest
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Keywords: Asthma; Molecular targeted therapy; Clinical decision-making; Severe uncontrolled asthma; Exacerbations

INTRODUCTION

Asthma is one of the most common respiratory diseases worldwide [1]. Its prevalence increased by 12.6% to 358.2 million individuals from 1990 to 2015, although mortality due to asthma decreased by 26.7% during this period [1]. Inhaled corticosteroids (ICS) provide better asthma control and reduce severe asthma exacerbations and mortality [2]. However, 5%–10% of patients are still suffer from asthma symptoms despite receiving extensive treatment and are diagnosed with severe uncontrolled asthma [2, 3]. Such patients often require biologics or bronchial thermoplasty (Bio/BT) to improve their asthma control. Guidelines mention the definition of severe uncontrolled asthma, which is used when considering Bio/BT introduction in such patients [3-6].

According to the European Thoracic Society/American Thoracic Society (ERS/ATS) severe asthma guidelines, patients are diagnosed with severe uncontrolled asthma if they exhibit at least one of the following 4 characteristics, despite extensive treatment including high dose ICS: (1) poor symptom control: asthma control questionnaire ≥ 1.5 or asthma control test (ACT) < 20; (2) frequent exacerbations: ≥2/yr bursts of systemic corticosteroids (3 days each), (3) serious exacerbations (admissions): ≥1/yr, and (4) airflow limitation: forced expiratory volume in 1 second (FEV_1) < 80% of predicted (%FEV_1 < 80%) following withholding of both short- and long-acting β_2 agonists (SABAs and LABAs, respectively) [3]. This definition of severe uncontrolled asthma is well established and commonly used to evaluate a patient's condition. However, these definitions are particularly important when considering the introduction of BT/Bio in patients with severe uncontrolled asthma.

This study aimed to clarify the characteristics of patients who need future use of Bio/BT using the ERS/ATS guidelines. Furthermore, we investigated the following biomarkers as potential indicators of Bio/BT requirements: absolute eosinophil and neutrophil counts (absolute eosinophil count [AEC] and absolute neutrophil count [ANC], respectively), serum total immunoglobulin E (IgE), fractional nitric oxide (FeNO), and capsaicin cough reflex sensitivity (C-CS).

MATERIALS AND METHODS

Patients

This is a *post hoc* analysis of our previous study regarding the association between C-CS and the clinical features of severe asthma [7]. We prospectively recruited 157 asthma patients who visited our hospital between November 2016 and October 2019. Of these 157 patients, 107 were classified into treatment step 4 according to the Global Initiative for Asthma (GINA) 2015 guidelines [5] and were analyzed in this study. Detailed information on the inclusion and exclusion criteria has been previously described [7]. The authors declare that this research was conducted in accordance with the World Medical Association Declaration of Helsinki. This study was approved by the ethics committee of Nagoya City

University (Number 1273) and registered in the UMIN Clinical Trials Registry (Registry ID UMIN000024734). Written informed consent was obtained from all the participants.

Measurements

Patients underwent blood tests, measurement of FeNO, spirometry, and capsaicin cough challenge test in that order between 9:00 AM and 1:00 PM. They also completed an ACT. The presence or absence of 6 comorbidities (rhinitis, chronic rhinosinusitis, conjunctivitis, atopic dermatitis, gastroesophageal reflux disease, and diabetes mellitus [DM]) were also ascertained through interviews with patients at that time. Detailed information on the measurements has been described previously [7]. Briefly, we analyzed AEC, ANC, serum total IgE levels, and serum-specific IgE against 8 aeroallergens using collected blood samples. Patients were considered nonatopic when all the specific IgE antibodies were negative (<0.35 IU/mL). We used ACT to evaluate asthma control. ACT consists of 5 items, with total scores ranging from 5 (worst) to 25 (best). Patients were considered poorly controlled if the ACT scored <20 [3, 8]. FeNO levels (at an oral expiratory flow rate of 50 mL/sec) were measured using a Sievers NOA 280i chemiluminescence analyzer (GE Analytical Instruments, Boulder, CO, USA) [9]. Spirometry was performed using the Chestac-8900 (Chest, Tokyo, Japan) according to the ERS/ATS guidelines [10]. To maintain ICS adherence, patients were asked not to withdraw long-acting β_2 agonists in combination with ICS (ICS/LABAs) prior to spirometry. Patients were considered as having airflow limitation if FEV_1 was <80% of the predicted value. All patients underwent capsaicin cough challenge test following spirometry to evaluate C-CS [7, 11-13]. We applied a dose-response fixed-time method using the Astograph (CHEST, Tokyo, Japan). Briefly, patients inhaled physiological saline for 1 minute followed by 10 doubling concentrations of capsaicin (0.61 to 312.5 μM) for 15 seconds per concentration at 1-minute intervals in increasing order. Patients also inhaled saline for 45 seconds between capsaicin doses to blind the patient from the change in dose. The test was terminated following the 45-second saline inhalation if the patient coughed 5 times or more and immediately inhaled SABAs for 2 minutes to ensure safety. We recorded the concentrations required to evoke at least 2 and 5 coughs (C2 and C5, respectively). We adopted the value of C5 as an index for C-CS. Lower C5 values represent heightened C-CS. We considered patients with heightened C-CS to have a value of C5 ≤ 2.44 μM [7].

Characteristics of severe uncontrolled asthma

Four characteristics of severe uncontrolled asthma were assessed in this study [3]. Apart from the ACT scores and the value of FEV_1 (%predicted), we counted the number of asthma exacerbations and admissions within 1 year prior to evaluation. Asthma exacerbations were defined as worsening asthma symptoms requiring oral corticosteroids for ≥3 days and/or intravenous corticosteroids for ≥1 day. Admissions were counted only when patients were admitted to the hospital because of asthma exacerbation. We counted the number of positive criteria for severe uncontrolled asthma for each patient.

Introduction of Bio/BT

The need for Bio/BT treatments was determined by asthma specialists (YK, KF, MT, and AN). The 4 characteristics of severe uncontrolled asthma [3] were not used to evaluate whether patients required Bio/BT treatments. The criteria for each treatment were as follows: omalizumab, serum IgE levels ranging from 30 to 1,500 IU/mL, and one or more positive specific IgE antibodies against aeroallergen; mepolizumab and benralizumab: AEC ≥ 300 /μL within 12 months prior to treatment initiation; and BT, patients did not meet the indication for omalizumab, mepolizumab, or benralizumab but required an additional intensive treatment.

Statistical analysis

Data were analyzed using JMP software (ver. 14.0; SAS Institute Inc., Tokyo, Japan). Data are presented as median (interquartile range). Categorical variables are presented as number (%). Higher C-CS (C5 ≤ 2.44 μM) [7], higher ANC (≥5,000/μL) [14], higher AEC (≥250/μL) [14], and higher FeNO (≥25 ppb) [9] were used as categorical variables. We divided patients into 2 groups: those who were treated with Bio/BT (Bio/BT+) and those who were not treated (Bio/BT-) within 3 months of evaluation. Furthermore, patients in the Bio/BT+ group were subdivided into Bio+ and BT+ groups to perform a sensitivity analysis. We compared all biomarkers and the 4 characteristics of severe uncontrolled asthma between the 2 groups using the Wilcoxon rank-sum test or Fischer exact test. We conducted multivariate logistic regression analysis to determine which of the 4 characteristics of severe uncontrolled asthma influenced the introduction of Bio/BT. We adopted the adjusted R_2 value as an index of the effect size. Values ≥0.25 and ≥0.64 indicate moderate and strong effects, respectively [15]. We repeated this analysis, including all clinical indices and biomarkers with a p value < 0.10 along with the 4 characteristics. We evaluated the correlation between the number of positive severe uncontrolled asthma criteria and each biomarker by using Spearman correlation coefficients. A p value ≤ 0.05 was considered significant when the α error was set at 5%.

RESULTS

Table 1 shows the patient characteristics. Fifteen patients received Bio/BT treatment within 3 months of the study measurements. Bio/BT treatments were categorized as follows: omalizumab (n = 4), mepolizumab (n = 3), benralizumab (n = 2), and BT (n = 6).

Table 1. Patients characteristic

Characteristic	All patients (n = 107)	Bio/BT- (n = 92)	Bio/BT+ (n = 15)	p value
Age (yr)	55 (44–70)	55 (44–69)	55 (45–71)	0.53
Female sex	74 (69.2)	61 (66.3)	13 (86.7)	0.14
Body mass index (kg/m^2)	22.5 (20.5–25.8)	22.5 (20.6–25.7)	23.0 (20.1–26.3)	0.80
Atopic predisposition, nonatopic*	34 (31.8)	27 (29.4)	7 (46.7)	0.23
Smoking, never/ex	76 (71.0)/31 (29.0)	67 (72.8)/25 (27.2)	9 (60.0)/6 (40.0)	0.36
Pack-years†	7.5 (2.0–28.0)	5.0 (1.3–14.0)	28.8 (13.4–50.5)	0.008
Pack-years >10	11 (10.3)	6 (6.5)	5 (33.3)	0.008
ICS (μg), daily	640 (500–900)	640 (500–750)	1,000 (960–1,500)	0.0001
Features of severe uncontrolled asthma				
ACT (point)	21 (17–24)	22 (19–24)	14 (12–15)	<0.0001
ACT <20	43 (40.2)	29 (31.5)	14 (93.3)	<0.0001
No. of exacerbation	0 (0–0)	0 (0–0)	2 (0–4)	<0.0001
Exacerbations ≥2/yr	16 (15.0)	6 (6.5)	10 (66.7)	<0.0001
No. of admissions	0 (0–0)	0 (0–0)	0 (0–2)	<0.0001
Admissions, ≥1/yr	8 (7.5)	1 (1.1)	7 (46.7)	<0.0001
FEV_1 (%predicted)	95.5 (86.1–107.5)	97.6 (87.0–108.9)	88.4 (73.7–101.5)	0.07
%FEV_1 <80	20 (18.7)	15 (16.3)	5 (33.3)	0.15
Positive numbers of the criterion	0 (0–1)	0 (0–1)	2 (1–3)	<0.0001
Comorbidities, presence				
Allergic rhinitis	60 (56)	50 (54)	10 (67)	0.42
Chronic rhinosinusitis	25 (23)	20 (22)	5 (33)	0.33
Conjunctivitis	7 (7)	5 (5)	2 (13)	0.25
Atopic dermatitis	6 (6)	5 (5)	1 (7)	>0.99
Gastroesophageal reflux disease	35 (33)	31 (34)	4 (27)	0.77
Diabetes mellitus	11 (10)	7 (8)	4 (27)	0.046

Values are presented as number (%) or median (range) and compared using the Wilcoxon rank-sum test and Fischer exact test.
Bio/BT, biologic agents or bronchial thermoplasty; ICS, inhaled corticosteroids; ACT, asthma control test; FEV_1, forced expiratory volume in 1 second.
*Patients were considered nonatopic when all specific IgE antibodies were negative at the <0.35 UA/mL. Otherwise, atopic. †n = 31 (Bio/BT -/+: 25/6).

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The proportion of patients with a smoking history of >10 pack-years and DM was greater in the Bio/BT+ group than in the Bio/BT- group. There were no significant differences in age, sex, body mass index, or atopic predisposition between the 2 groups. The Bio/BT+ group had higher daily ICS doses, reported worse asthma control, and experienced more frequent exacerbations and admissions than the Bio/BT- group. FEV_1 was marginally, but insignificantly, lower in the Bio/BT+ group than in the Bio/BT- group. The median number of positive criteria for severe uncontrolled asthma in the Bio/BT+ group was 2 (1–3), which was significantly higher than that in the Bio/BT- group.

Comparison of biomarkers between the Bio/BT+ and the Bio/BT- groups

We compared the biomarker results between the Bio/BT+ and Bio/BT- groups (**Table 2**). The Bio/BT+ group showed lower C2 and C5 values than the Bio/BT- group. The prevalence of patients with heightened C-CS (C5 ≤ 2.44 μM) was greater in the Bio/BT+ group than in the Bio/BT- group. ANC was also greater in the Bio/BT+ group than in the Bio/BT- group; however, there was no difference in the number of patients with high ANC (≥5,000/μL) between the 2 groups. Levels of type 2 inflammation-related biomarkers, such as AEC, serum IgE, and FeNO, were also similar between the 2 groups.

Patients in the Bio/BT+ group were subdivided into Bio+ and BT+ groups to perform a sensitivity analysis (**Supplementary Table 1**). Compared with the Bio/BT- group, patients in the Bio+ group had lower lung function and higher levels of AEC, serum total IgE, and FeNO; however, those in the BT+ group had lower levels of serum total IgE and lower values of C2 and C5. Type 2 inflammation-related biomarkers were significantly higher in the Bio+ group than in the BT+ group. There were no significant differences in the 4 definitions of severe uncontrolled asthma between patients in the Bio+ group and those in the BT+ group. The results indicate that type 2 inflammation-related biomarkers are available for the selection of treatment (Bio or BT) of patients with severe uncontrolled asthma, and the 4 characteristics themselves did not affect treatment decision-making.

We also assessed the breakdown of 4 characteristics in patients in the Bio+ and BT+ group, respectively (**Table 3**). Eight patients in the Bio+ group were poor asthma control. Among 8 patients with poor asthma control, 7 experienced frequent exacerbations. Three of 7 also experienced admissions. One patient without poor asthma control had the history of admissions and airflow limitation. One patient was poor asthma control without frequent exacerbations, admissions or airflow limitation. Meanwhile, all 6 patients in the BT+ group were poor asthma control. Three had both the history of frequent exacerbations and

Table 2. Comparisons of biomarkers between Bio/BT+ and Bio/BT- groups

Biomarker	All patients (n = 107)	Bio/BT- (n = 92)	Bio/BT+ (n = 15)	*p* value
C2 (μM)*	4.88 (1.22–19.52)	9.76 (1.22–19.52)	2.44 (1.22–4.88)	0.04
C5 (μM)*	9.76 (2.44–39.0)	19.52 (4.88–39.0)	2.44 (1.22–9.76)	0.03
C5 ≤2.44 μM	30 (28.0)	22 (23.9)	8 (53.3)	0.03
AEC (/μL)	122 (65–263)	118 (66–241)	184 (51–772)	0.24
AEC ≥250 /μL	28 (26.2)	22 (23.9)	6 (40.0)	0.21
ANC (/μL)	3,413 (2,529–4,217)	3,328 (2,404–4,063)	3,807 (3,457–4,759)	0.009
ANC ≥5,000 /μL	10 (9.4)	7 (7.6)	3 (20.0)	0.15
Serum IgE (IU/mL)	107 (38–354)	106 (40–371)	228 (23–326)	0.84
FeNO (ppb)	20.6 (14.6–32.9)	20.0 (14.3–32.1)	24.2 (20.4–40.6)	0.16
FeNO ≥25 ppb	37 (34.6)	31 (33.7)	6 (40.0)	0.77

Values are presented as number (%) or median (interquartile range) and compared using the Wilcoxon rank-sum test and Fischer exact test.
Bio/BT, biologic agents or bronchial thermoplasty; AEC, absolute eosinophil count; ANC, absolute neutrophil count; FeNO, fractional nitric oxide.
*Concentrations required to induce at least 2 (C2) or 5 coughs (C5).

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Table 3. The breakdown of 4 characteristics of the ERS/ATS definition in patients in the Bio+ and BT+ groups

Characteristic	Bio (n = 9)		BT (n = 6)	
	Applicable	Not applicable	Applicable	Not applicable
Asthma control (ACT < 20)	8	1	6	0
Exacerbations (≥2/yr)	7	2	3	3
Admissions (≥1/yr)	4	5	3	3
Airflow limitation (%FEV_1 < 80)	4	5	1	5

ERS/ATS, European Thoracic Society/American Thoracic Society; Bio+, biologic agents; BT+, bronchial thermoplasty; ACT, asthma control test.

admission, and one had airflow limitation. Two were poor asthma control without frequent exacerbations, admissions or airflow limitation.

The associated criteria of severe uncontrolled asthma in Bio/BT introduction

We further investigated the characteristics associated with the administration of Bio/BT treatment (**Table 4**). Multivariate regression analysis revealed that poor symptom control (ACT <20), frequent exacerbations (≥2/yr), and admissions (≥1/yr) contributed to the subsequent Bio/BT treatment. An adjusted R_2 value of 0.60 suggests that these 3 characteristics have a strong influence when considering the Bio/BT treatment of patients (model 1). Heightened C-CS, heavy smoking history (>10 pack-years), or the presence of DM had no significant effect on Bio/BT introduction when added to the multivariate analysis along with the 4 clinical characteristics (model 2). Frequent exacerbations (≥2/yr) and admissions (≥1/yr) were significant factors for the introduction of Bio/BT in both models 1 and 2. Similar results were obtained when the factors contributing to Bio introduction were analyzed (models 3 and 4 of **Supplementary Table 2**). AEC was not related to the indication for Bio (model 4 of **Supplementary Table 2**). These models indicate that frequent exacerbations and admissions are the most important factors when considering the use of Bio/BT in patients with severe uncontrolled asthma. We did not perform multivariate analysis to determine the need for BT because of the small number of patients in the BT+ group (n = 6).

DISCUSSION

The present study evaluated the associated characteristics of the severe uncontrolled asthma with future Bio/BT. Although many factors, such as treatment cost, accessibility, physician's preference and experience, and patient's characteristics, may underline when considering introduction of such treatments, poor asthma control, frequent exacerbations, and admissions were associated with future use of Bio/BT. Indeed, most of patients who were

Table 4. Factors contributing to determine Bio/BT introduction

Variable	Model 1			Model 2		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Asthma control (ACT < 20)	13.0	1.2–144.0	0.04	10.1	0.8–133.0	0.08
Exacerbations (≥2/yr)	6.2	1.2–33.6	0.03	6.5	1.1–37.4	0.04
Admissions (≥1/yr)	41.5	1.8–978.0	0.02	47.4	1.7–1,296.0	0.02
Airflow limitation (%FEV_1 < 80)	1.1	0.2–7.0	0.94	2.0	0.2–18.9	0.56
C5 ≤2.44 μM, presence	-	-	-	3.0	0.5–18.3	0.24
Pack-years >10, presence	-	-	-	1.01	0.08–12.2	0.99
Diabetes mellitus, presence	-	-	-	0.61	0.05–7.1	0.70
Effect size	R^2 = 0.60			R^2 = 0.62		

Model 1 included only 4 clinical characteristics of severe uncontrolled asthma: Model 2 included heightened C-CS (capsaicin cough reflex sensitivity, ≤2.44 μM), heavy smoking history (>10 pack-years), and diabetes mellitus in addition to model 1.
Bio, biologic agents; BT, bronchial thermoplasty; OR, odds ratio; CI, confidence interval; ACT, asthma control test; FEV_1, forced expiratory volume in 1 second.

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introduced Bio/BT experienced frequent exacerbations and/or admissions (n = 8 [88.9%] for the Bio group, and n = 3 [50%] for the BT group, respectively).

Unlike poor asthma control, frequent exacerbations, and admission, airflow limitation was not associated with subsequent introduction of Bio/BT in the present study. Persistent asthma symptoms and severe asthma exacerbations are known factors of airflow limitation and pulmonary function decline in patients with asthma [16]. However, airflow limitation is not always associated with poor asthma control or exacerbations [17, 18]. It has been reported that only 25% of patients with poorly controlled asthma have airflow limitation [17]. In an epidemiological study of patients with severe asthma, admissions, emergency department visits, poor asthma control, and the need for oral corticosteroid bursts were significant risk factors for severe asthma exacerbation [18]. In contrast, lung function does not affect severe asthma exacerbations [18]. In a 26-year follow-up longitudinal study of patients with asthma, patients who developed irreversible airway obstruction had a lower frequency of asthma exacerbations [19]. Airflow limitation may contribute to severe uncontrolled asthma in a manner that is different from the other 3 characteristics.

There was no difference among the type 2 biomarkers tested between the Bio/BT+ and Bio/BT- groups in this study. AEC and atopic predisposition are important clinical indices for indication and selection of biologics. However, the Severe Asthma Research Program study demonstrated that type 2 biomarkers such as AEC, serum IgE, and FeNO were unrelated to disease severity [20]. This may be explained by the fact that type 2 airway inflammation is affected by ICS to a certain extent in most patients. In addition, burst administration of systemic corticosteroids due to asthma exacerbation results in an increase in neutrophils, a decrease in eosinophils, and the onset of DM. Therefore, the difference in ANC levels and the prevalence of DM between the 2 groups may be an epiphenomenon. In contrast, the present findings suggest that C-CS might be refractory to corticosteroids, unlike eosinophilic inflammation, as we previously indicated that C-CS in asthma was not changed by ICS [13]. Although heightened C-CS, DM, and smoking are associated with the pathophysiology of severe asthma [7], they did not affect the prediction of future Bio/BT introduction. This outcome may indicate that the pathophysiology of severe uncontrolled asthma is formed by a complex of several clinical, morphological, and molecular mechanisms [21]. Therefore, any specific biomarkers or comorbidities cannot indicate future Bio/BT use in patients with severe asthma.

The present study had some limitations. First, we did not evaluate whether the use of Bio/BT is beneficial to patients. Therefore, we cannot state that the ERS/ATS definition of severe uncontrolled asthma is useful in selecting patients for whom Bio/BT would be beneficial. Longitudinal observational studies are necessary to assess the utility of the ERS/ATS definition of severe uncontrolled asthma as a tool for predicting Bio/BT responses. Second, the number of patients was relatively small because this single-center study only included patients classified as treatment step 4 according to the GINA 2015 guidelines. Additionally, the present results were obtained from the experience of a single center. The prescription of Bio/BT may depend on the preference and experience of physicians. Other factors, such as treatment cost, accessibility, and patient's characteristics, also affect treatment decision-making. Indeed, treatment indications are substantially different between biologics and bronchial thermoplasty. Thus, treatment bias may affect results of the present study. Nonetheless, the ERS/ATS definition would be a succinct tool when considering an additional intensive treatment to patients whose asthma condition are unstable despite taking conventional treatments such as high dose ICS and long-acting β_2 agonists. Further

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cohort studies are required to confirm our findings. Third, biologics and BT differ in their mechanisms of action and indications. Thus, there may be different characteristics of clinical background and biomarkers between patients in the Bio+ and BT+ groups. Type 2 biomarkers, such as AEC, serum IgE, and FeNO are available when selecting Bio or BT for patients in clinical practice. Indeed, patients in the Bio+ group had higher levels of type 2 inflammation-related biomarkers than those in the Bio group (**Supplementary Table 1**). However, a history of frequent exacerbations (≥2/yr) and admissions (≥1/yr) would be useful in selecting patients who need an additional intensive treatment, irrespective of the clinical phenotypes of severe uncontrolled asthma. The proportion of patients who experienced frequent exacerbations (≥2/yr) and admissions (≥1/yr) was similar between patients in the Bio+ and BT+ groups, but these 2 groups experienced exacerbations including admissions more than those in the Bio/BT- group (**Supplementary Table 1**). Despite these limitations, clinicians can objectively consider the need for Bio/BT in patients with severe uncontrolled asthma by evaluating asthma control and the history of severe exacerbations requiring systemic corticosteroids and admissions based on the ERS/ATS definition.

In conclusion, the present study demonstrated the associated characteristics of patients with severe uncontrolled asthma whose further intensive treatment was required. Poor asthma control, frequent exacerbations, and admissions are important factors to be considered when introducing Bio/BT. Clinicians may consider an additional Bio/BT treatment if patients with severe asthma have poor asthma control and experience severe exacerbation requiring frequent administration of systemic corticosteroids (≥2/yr) or hospitalization due to asthma within 1 year. Although multiple factors such as treatment cost and asthma phenotypes affect treatment decision-making, the ERS/ATS definition of severe uncontrolled asthma would be helpful to assess such factors. The present results would provide useful information for clinicians regarding the management of severe uncontrolled asthma.

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SUPPLEMENTARY MATERIALS

Supplementary Tables 1 and 2 can be found via **10.5415/apallergy.2022.12.e13**

Supplementary Table 1

Comparison of clinical characteristics and biomarkers between patients in the Bio/BT- and those in the Bio+ (A), those in the BT/Bio- and those in the BT+ (B), and those in the Bio+ and those in the BT+ groups (C)

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Supplementary Table 2

Factors contributing to determine Bio introduction

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