Allergy Asthma Immunol Res. 2024 May;16(3):253-266
https://doi.org/10.4168/aair.2024.16.3.253
pISSN 2092-7355·eISSN 2092-7363

Allergy, Asthma & Immunology Research AAIR

Original Article

Real-World Effectiveness of Biologics in Patients With Severe Asthma: Analysis of the KoSAR

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Received: Sep 21, 2023
Revised: Jan 3, 2024
Accepted: Jan 26, 2024
Published online: Apr 29, 2024

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Disclosure

There are no financial or other issues that might lead to conflict of interest.

ABSTRACT

Purpose: Severe asthma is associated with high morbidity and healthcare utilization; however, treatment options for these patients are limited. This study aimed to determine the therapeutic effects of biologics in clinical practice.

Methods: This multicenter, retrospective cohort study included 136 patients who received biologics for at least 4 months between September 2017 and July 2022 at 25 medical centers affiliated with the Korean Severe Asthma Registry (KoSAR). The study evaluated the treatment effects, including acute exacerbation rates, maintenance of oral corticosteroid dosages, lung function, quality of life, blood eosinophil count, and fractional exhaled nitric oxide (FeNO) levels, by comparing measurements before and after 4 months of biologic treatment. Responses for each medication was evaluated based on the Global Evaluation of Treatment Effectiveness score, and any adverse reactions were summarized.

Results: With the administration of biologics over the course of 4 months, there was a reduction in asthma acute exacerbations, a significant improvement in lung function, and a significant decrease in daily maintenance dose of oral steroid. Blood eosinophil counts decreased in the mepolizumab and reslizumab groups, while FeNO levels decreased only in the dupilumab group. The Asthma Control Test, Quality of Life Questionnaire for Adult Korean Asthmatics, and the EuroQol-visual analogue scale scores showed a significant improvement. Most patients (80.15%) responded to the biologic treatment. Meanwhile, non-responders often had chronic rhinosinusitis as a comorbidity, exhibited lower lung function, and required higher doses of oral steroids. No severe adverse events were reported.

Conclusions: Biologics are highly effective in Korean patients with Type 2 severe asthma, significantly reducing acute exacerbation rates and doses of oral corticosteroids, while also improving lung function. Therefore, it seems beneficial to administer biologics without any restrictions to patients exhibiting Type 2 severe asthma.

Keywords: Asthma; eosinophils; lung function; rhinosinusitis; mepolizumab; reslizumab; dupilumab; omalizumab

INTRODUCTION

Severe asthma (SA) is characterized as uncontrolled asthma despite adherence to maximal optimized high dose inhaled corticosteroids/long-acting beta2-antagonist (ICS/LABA) or correction of modifiable factors.[1] Patients with SA experience a very poor quality of life and incur high medical costs due to frequent exacerbation, high-dose medication use, and frequent visits to medical institutions.[2,3] The development of biologics targeting type 2 (T2) inflammation brings a new inflection to the treatment of SA.[4] These biologics have demonstrated efficacy in decreasing acute exacerbation, reducing oral corticosteroid maintenance dose, and improving lung function and asthma control in pivotal randomized controlled trials (RCTs).[5-11] However, these RCTs are conducted under highly controlled environments. Therefore, real-world studies are important because they encompass various clinical characteristics such as age, socioeconomic status, smoking status or comorbidities.[12-14]

SA registries are observational studies that follow patients, providing real-world evidence and serve as an important tool for evaluating the effectiveness of biologics.[13] There are many regional, national, and global registries for evaluating the real-world effectiveness of biologics in SA. Examples of such registries include the UK Severe Asthma Registry (UKSAR),

Severe Heterogeneous Asthma Research Collaboration Patient Centered (SHARP), German Asthma Net (GAN), Severe Asthma Network in Italy (SANI), and International Severe Asthma Registry (ISAR).[15-19] Additionally, there is a national registry of SA in Korea known as the Korean Severe Asthma Registry (KoSAR; https://www.severeasthmawg.com/). Furthermore, there is a subgroup within KoSAR called KoSAR-BIO, consisting of patients receiving biologics.[20] In the unique medical environment of Korea, this study was designed using the information of patients registered with KoSAR-BIO to identify the most effective treatment for Korean patients with SA. This involved analyzing prescribing pattern, treatment effect, and adverse reactions during biologic treatments.[20]

In this study, we aimed to estimate the effectiveness of biologics in patients with SA and identify predictive factors for the response to biologic treatment among those enrolled in KoSAR-BIO.

MATERIALS AND METHODS

Patients and study design

This multicenter, retrospective study included patients who received biologics for uncontrolled SA for > 4 months between September 2017 and July 2022 in 25 medical centers affiliated to the KoSAR-BIO.[20] Benralizumab was the latest drug approved by the Ministry of Food and Drug Safety (MFDS). Therefore, only 4 biologics (mepolizumab, reslizumab, dupilumab, and omalizumab) were included in the analysis. The baseline for the study was set as the first day of biologic administration, and follow-up data were collected on each subsequent day of administration. Most data were collected on a monthly basis, except for dupilumab, due to its different dosing interval.

Informed consent was obtained from all participants. The study was performed in accordance with the Declaration of Helsinki, and the protocols were approved by the Institutional Review Board of each participating centers.

Treatment outcomes and responder evaluation

Baseline characteristics were collected from all patients. In addition, to evaluate the effects of biologics, the number of acute exacerbations, oral corticosteroid maintenance dose, lung function, Asthma Control Test (ACT), and quality of life score (Quality of Life Questionnaire for Adult Korean Asthmatics [QLQAKA] and EuroQol-Visual Analogue Scale [EQ-VAS])[21] were collected on a monthly basis. Acute exacerbation was defined as an unscheduled outpatient visit, emergency room visit, hospitalization, admission to the intensive care unit (ICU), or burst administration of systemic steroids with ≥ 15 mg for ≥ 3 days.

A responder was defined based on the Global Evaluation of Treatment Effectiveness (GETE) score, judged by the physician. Patients with excellent or good GETE scores were defined as responders, whereas those with moderate, poor, or worsening GETE scores were defined as non-responders.[22]

Adverse reactions

Data on adverse reactions that occurred during the administration of biologics were also collected. The severity of these reactions was categorized into mild, moderate, or severe. A mild reaction was defined as a case in which symptoms occurred; but the patient could continue

https://doi.org/10.4168/aair.2024.16.3.253

taking the drug without affecting his/her daily life. Moderate severity was defined as the degree to which dose reduction or change in medication was necessary because it affected the patient's daily life. Severe reactions were defined as side effects that required discontinuation of the drug.[23] These adverse reactions were collected after each dose administration.

Statistical analysis

All statistical analyses were performed using SAS 9.4 (SAS Institute, Cary, NC, USA) and R software (R Project for Statistical Computing, Vienna, Austria; www.r-project.org/). For descriptive statistics, continuous variables were presented as means ± standard deviations (SD) or medians with interquartile ranges, and as counts of events (%) for categorical variables. One-way analysis of variance or the Kruskal-Wallis test was used to compare the means of more than 2 groups for parametric or nonparametric data, respectively. To assess the effects of the biologics on paired comparison, parametric data were analyzed using the paired *t*-test, and nonparametric data were compared using the Wilcoxon signed-rank test. Statistical significance was defined as a two-sided *P* value of < 0.05.

RESULTS

Clinical characteristics of patients

We enrolled 191 patients from the KoSAR registry who received biologics treatment. Of these, 136 patients received the biologic injections for at least 4 months. Information from these patients was used to compare the effects before and after biologic treatment. Based on the first drug administered, 42, 52, 17, and 25 patients received mepolizumab, reslizumab, dupilumab, or omalizumab, respectively. The baseline characteristics of the patients according to the first administration of biologics are presented in **Table 1**. The mean age of the patients was 52.7 years, and those receiving dupilumab and omalizumab had a younger mean age. Regarding the distribution of sex particularly in the reslizumab group, there were more women than men (73.1%). More than half of the patients were never-smokers, and the proportion of patients currently smoking was not high (≤ 5%, except for the dupilumab group). The onset age of asthma was the lowest in the omalizumab group (32.1 ± 16.7 years old), followed by the dupilumab group (39.2 ± 12.7 years old). There was no significant difference between groups in terms of the mean number of acute exacerbations during the past year, and the reslizumab group showed the highest mean ± SD (3.4 ± 4.1). The ACT scores were less than 20 points in all groups, and allergic rhinitis and chronic sinusitis were identified as comorbidities. Among the comorbidities, the incidence of nasal polyps was the highest in the reslizumab group (17.4%). Mean lung function, based on forced expiratory volume one second (FEV1), was 67.6% (66.4%–69.8%). Both fractional exhaled nitric oxide (FeNO; mean, 61.1 ppb) and blood eosinophils (610 cells/μL) showed characteristics of high T2 inflammation. The proportion of oral corticosteroids (OCS)-dependent patients with asthma was 27.9%, and the average daily OCS dose was 2.8 ± 5.0 mg. The mepolizumab group showed the highest rate of OCS maintenance, and the mean daily OCS maintenance dose was the highest at 4.1 ± 5.1 mg. The omalizumab group shows the lowest daily OCS maintenance dose at 0.9 ± 1.8 mg (**Table 1**).

Biologics effectiveness: severe exacerbation, pulmonary function, and OCS maintenance

The annual incidence of severe acute exacerbations in all patients receiving biologics significantly reduced from 2.5 to 0.2 (92% reduction; $P < 0.001$). The reduction varied

https://doi.org/10.4168/aair.2024.16.3.253

Table 1. Baseline clinical characteristics of patients according to first administration of biologics

Characteristics	Total (n = 136)	Mepolizumab (n = 42)	Reslizumab (n = 52)	Dupilumab (n = 17)	Omalizumab (n = 25)	*P* value
Age (yr)	52.7 ± 11.7	52.6 ± 11.9	56 ± 9.7	49.9 ± 13.3	47.9 ± 12.4	**0.023**
Female	75 (55.1)	17 (40.5)	38 (73.1)	7 (41.2)	13 (52.0)	**0.008**
BMI (kg/m^2)	24.9 ± 4.1	24.4 ± 3.7	24.5 ± 3.6	24.8 ± 4.2	26.5 ± 5.5	0.168
Smoking						0.385
Never smoker	74 (54.4)	20 (47.6)	32 (61.5)	7 (41.2)	15 (60.0)	
Ex-smoker	45 (33.1)	18 (42.8)	12 (23.1)	6 (35.3)	9 (36.0)	
Current smoker	7 (5.1)	2 (4.8)	2 (3.8)	2 (11.8)	1 (4.0)	
Asthma onset age (yr)	40.5 ± 14.7	42.9 ± 13.4	42.5 ± 14.4	39.2 ± 12.7	32.1 ± 16.7	**0.043**
Asthma control						**< 0.001**
Uncontrolled	40 (29.4)	11 (26.2)	12 (23.1)	5 (29.4)	12 (48.0)	
Partly controlled	49 (36.0)	6 (14.3)	32 (61.5)	7 (41.2)	4 (16.0)	
Controlled	19 (14.0)	11 (26.2)	4 (7.7)	2 (11.8)	2 (8.0)	
Asthma exacerbations over the past year	2.5 ± 3.5	2.3 ± 3.2	3.4 ± 4.1	1.4 ± 2.4	1.7 ± 3.2	0.120*
ACT score	16.8 ± 5.7	17.1 ± 5.7	17.4 ± 5.5	16.1 ± 7.5	15.3 ± 4.7	0.678
QLQAKA	56.7 ± 16	57.3 ± 14.6	58.5 ± 14.8	55.6 ± 21.1	51.6 ± 16.6	0.606
EQ-VAS	63.5 ± 21.1	62.7 ± 27.2	63.2 ± 21.8	65.5 ± 22.5	63.2 ± 10.6	0.990
Comorbidities						
Allergic rhinitis	101 (74.3)	33 (78.6)	38 (73.1)	9 (52.9)	21 (84.0)	0.250
Atopic dermatitis	18 (13.2)	3 (7.1)	7 (13.5)	3 (17.6)	5 (20.0)	0.556
Chronic rhinosinusitis	62 (45.6)	22 (52.4)	23 (44.2)	7 (41.2)	10 (40.0)	0.820
Nasal polyps	16 (11.8)	3 (7.1)	8 (15.4)	1 (5.9)	4 (16.0)	0.440
Pulmonary function test						
FEV1 (%)	67.6 ± 19	66.4 ± 16.5	67.1 ± 19.2	69.8 ± 25.2	69.3 ± 19	0.911
FEV1 (mL)	2,030.2 ± 767.3	2,116.3 ± 744.8	1,845.6 ± 559.9	2,330.7 ± 1,029.9	2,092.7 ± 955.3	0.115
FVC (%)	79.6 ± 14.2	78.4 ± 12.8	78.7 ± 13.4	82.9 ± 19.3	81.7 ± 14.7	0.618
FVC (mL)	3,019.5 ± 931.1	3,164.2 ± 904.2	2,758.6 ± 696.7	3,324.7 ± 1,013.7	3,146.4 ± 1,263.5	0.070
FEV1/FVC (%)	67.3 ± 13.8	67 ± 13.1	67.7 ± 13.8	68.6 ± 16.6	65.9 ± 13.7	0.943
FeNO (ppb)	61.1 ± 58.2	62.2 ± 67.8	59.5 ± 57	60.5 ± 42.2	65.3 ± 60.9	0.985*
Blood eosinophil (count)	610.7 ± 689	596.9 ± 589.6	631.8 ± 615.2	332.7 ± 181.7	811.1 ± 1,186.9	0.566*
Total IgE (IU/mL)	790.1 ± 825.8	484.8 ± 518.3	833.1 ± 822.6	801.7 ± 460.8	961.3 ± 1,159	0.931*
Medication						
Inhaled corticosteroids (mcg/day)†	888.9 ± 633.4	890 ± 598.9	760 ± 597.3	1,042.6 ± 715.9	1,072 ± 686.4	0.236*
OCS maintenance	38 (27.9)	16 (38.1)	14 (33.3)	3 (17.6)	5 (20.0)	0.844
OCS maintenance dose (mg/day)	2.8 ± 5	4.1 ± 5.1	2.6 ± 4.4	3.1 ± 8.2	0.9 ± 1.8	**< 0.001***

Continuous variables were presented as means ± standard deviations and categorical variables were presented as counts of events (%). The *P* values marked in bold indicate they are statistically significant.
BMI, body mass index; ACT, Asthma Control Test; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics; EQ-VAS, EuroQol-Visual Analogue Scale; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; OCS, oral corticosteroids.
*Nonparametric method (Kruskal-wallis test); †Budesonide equivalent dose.

depending on the specific biologic treatments as follows: the mepolizumab group, from 2.3 to 0.2 ($P < 0.001$); the reslizumab group, from 3.4 to 0.2 ($P < 0.001$); the dupilumab group, from 1.4 to 0.3 ($P = 0.078$); and the omalizumab group, from 1.7 to 0 ($P = 0.008$) (**Fig. 1**).

Pre-bronchodilator FEV1 (mL) improved after 4 months improved in biologic-treated patients (220 mL; $P < 0.001$) (**Fig. 2A**). The improvement in FEV1 (mL) was highest in the reslizumab group (380 mL, $P < 0.001$). The omalizumab group also showed a statistically significant improvement in FEV1 (320 mL; $P = 0.04$). The dupilumab group also showed improved FEV1, although it was not statistically significant (105 mL; $P = 0.35$). Pre-bronchodilator forced vital capacity (FVC) also improved (80 mL; $P < 0.001$) (**Fig. 2B**). The details of the changes in lung function are presented in **Supplementary Table S1**.

A total of 38 patients were under OCS maintenance for asthma. In these patients, OCS maintenance dose also showed a statistically significantly decrease after biologic administrations (2.8 ± 5.0 to 0.7 ± 2.0 mg/day; $P < 0.001$) (**Fig. 3**). A reduction of approximately more than 80.5% was confirmed in the mepolizumab group, which had

https://doi.org/10.4168/aair.2024.16.3.253

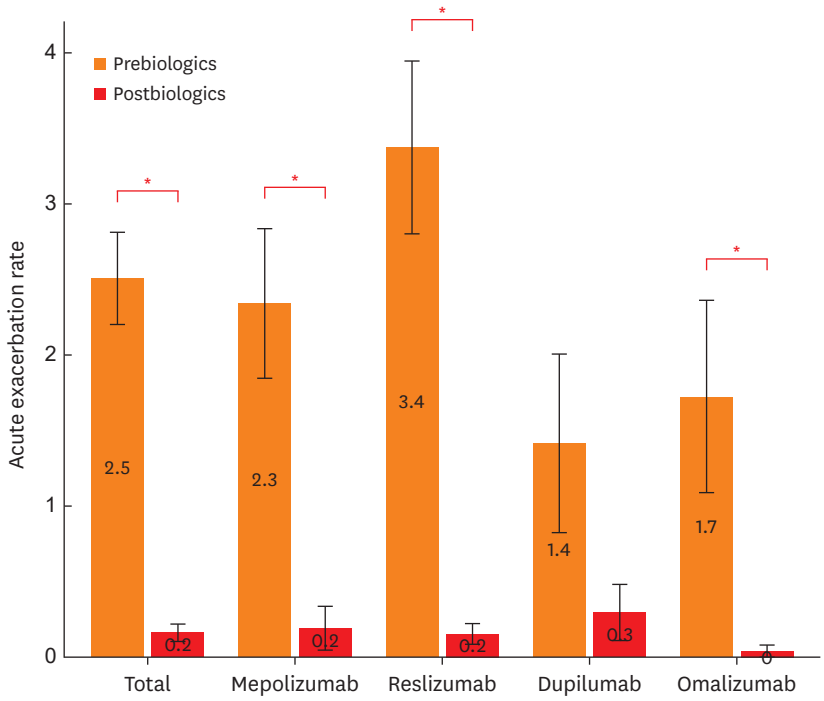

Fig. 1. Rate of acute exacerbation before and after the initiation of each biologic treatment The number of acute exacerbations decreased significantly.
*P < 0.05.

the highest dose prior to biologic treatment (4.1 ± 5.1 to 0.8 ± 1.7 mg/day, P < 0.001). The reslizumab group showed a reduction of 84.6% (2.6 ± 4.4 to 0.4 ± 0.8 mg/day, P < 0.001), and the dupilumab group showed a reduction of 83.9% (3.1 ± 8.2 to 0.5 ± 1.8 mg/day, P = 0.016). Only the omalizumab group showed a slight increase (0.9 ± 1.8 to 1.1 ± 3.7 mg/day, P = 0.094) (**Fig. 3**).

Biomarker of T2 inflammation

After biologic treatment, blood eosinophil count decreased (432.15 [203.6–760.6] to 94.2 [36.4–271.35], P < 0.001). However, a statistically significant decrease was observed in patients treated with mepolizumab (434.9 [209.2–722.0] to 100.3 [28–198.4], P = 0.013) or reslizumab (462.7 [204.7–886.2] to 58.5 [31.2–100.4], P < 0.001), which have anti-interleukin-5 mechanisms, while dupilumab and omalizumab showed a slight change (**Fig. 4A**). On the other hand, in the case of FeNO, only the dupilumab group showed a significant decrease (62 [16–91] to 14 [12–23] ppb, P = 0.001) (**Fig. 4B**).

Asthma control and quality of life

We evaluated asthma control and quality of life in patients using the ACT sore, QLQAKA, and EQ-VAS. Overall, there were improvements in the ACT, QLQAKA, and EQ-VAS scores after the administration of biologics. After biologic administration, the mean ACT, QLQAKA, EQ-VAS scores increased (16.8 vs.19.6 points, P = 0.003; 56.7 vs. 68.3 points, P < 0.001; and 63.5 vs. 73.9 points, P < 0.001, respectively). Among them, patients in the reslizumab group showed statistically significant improvements in all parameters (**Fig. 5**).

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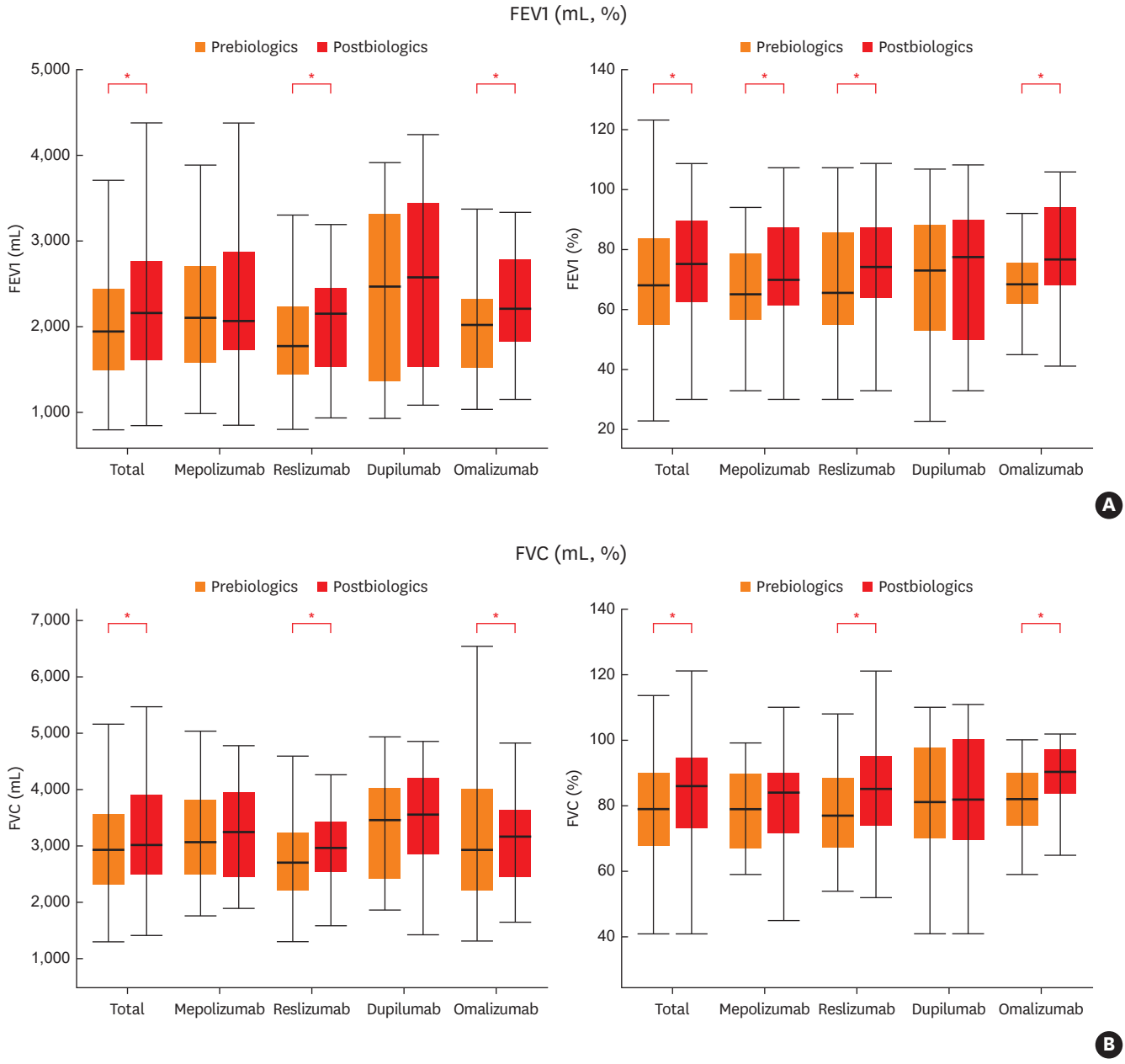

Fig. 2. Changes in pulmonary function before and after the initiation of each biologic treatment. (A) FEV1 (mL, %) and (B) FVC (mL, %).
This boxplot represents the median and interquartile ranges.
FEV1, forced expiratory volume one second; FVC, forced vital capacity.
*$P < 0.05$.

Responder and non-responder

Biologic responders were identified in 109 of 136 patients (80.2%), while non-responders were identified in 27 of 136 patients (19.9%). According to the specific medications, non-responders were identified in 15 of 42 patients (35.71%) in the mepolizumab group, 4 of 52 patients (7.69%) in the reslizumab group, 2 of 17 patients (11.76%) in the dupilumab group, and 7 of 28 patients (24.00%) in the omalizumab group (**Fig. 6**). Regarding the difference in the clinical characteristics between the responder and non-responder groups, the proportion of patients with chronic rhinosinusitis as a comorbidity was higher in the non-responder group (63% [n =

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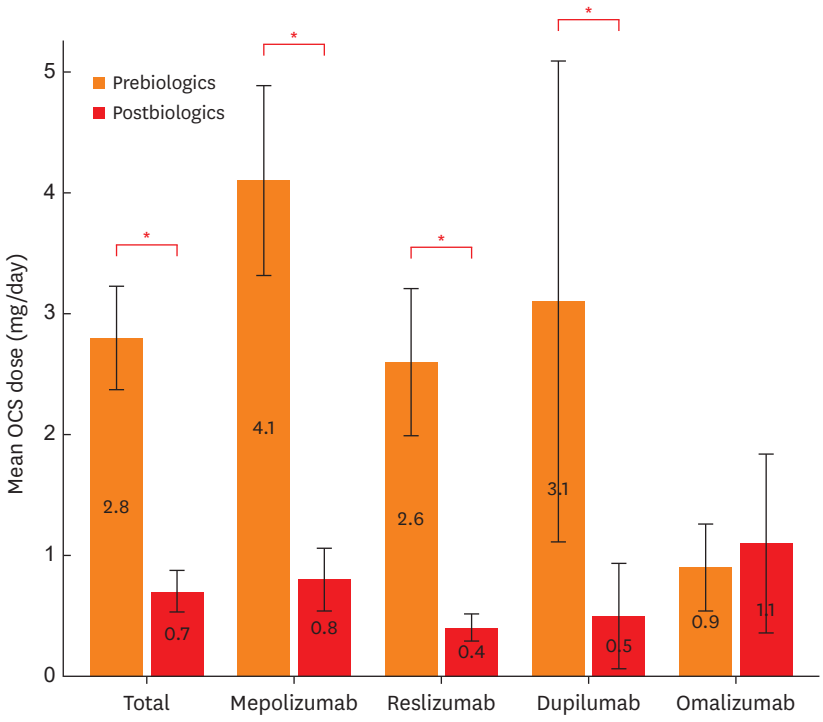

Fig. 3. Changes in the maintenance dose of OCS according to the biologics. The maintenance dose of OCS decreased significantly.
OCS, oral corticosteroids.
*$P < 0.05$.

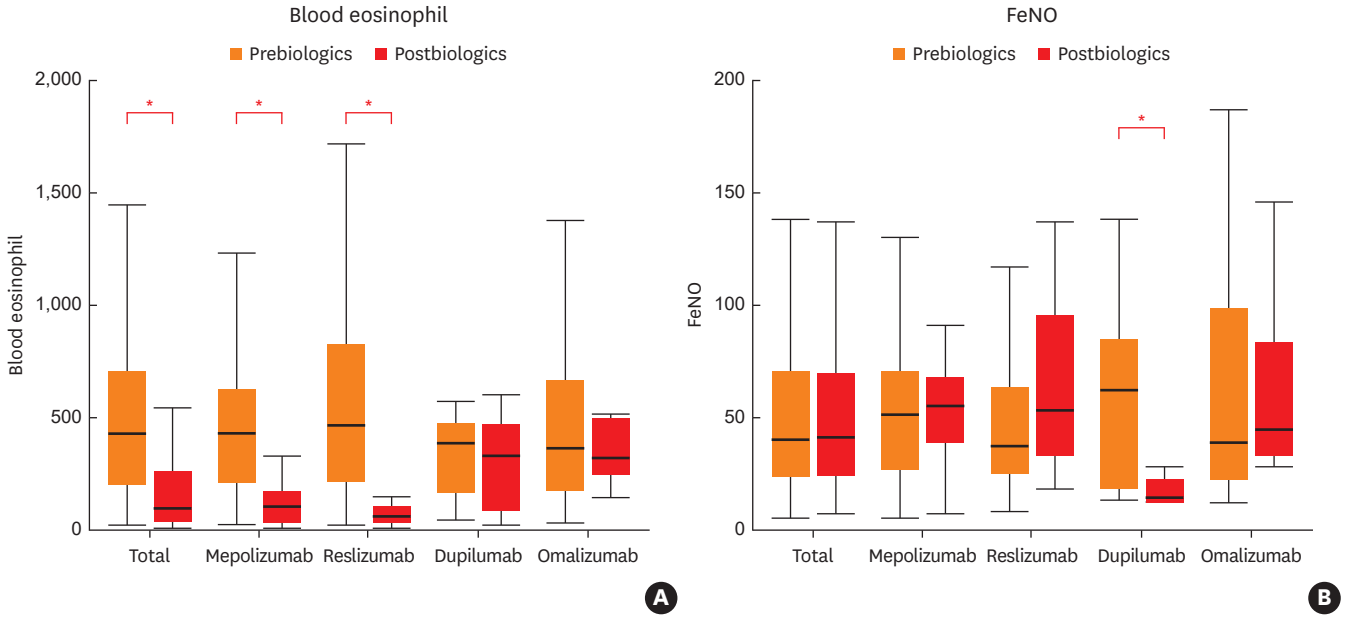

Fig. 4. Changes in T2 inflammation biomarkers. (A) Blood eosinophil count and (B) FeNO.
This boxplot represents the median and interquartile ranges.
T2, type 2; FeNO, fractional exhaled nitric oxide.
*$P < 0.05$.

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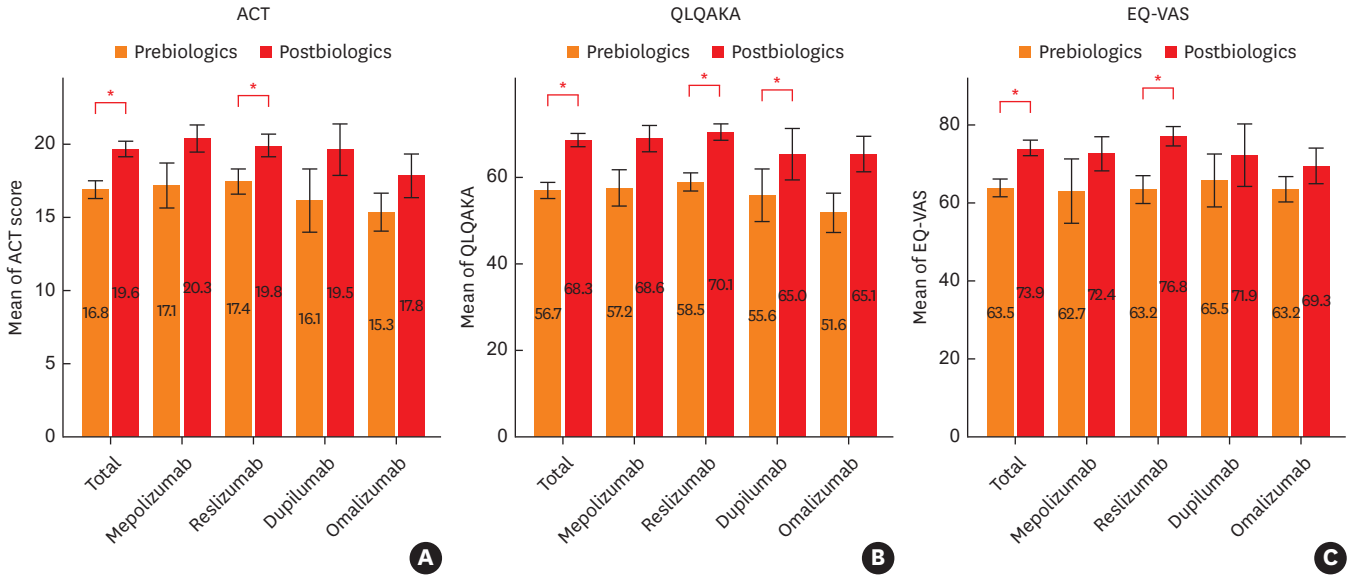

Fig. 5. Changes in asthma control and quality of life in patients with severe asthma treated with biologics. (A) ACT, (B) QLQAKA, and (C) EQ-VAS.
ACT, Asthma Control Test; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics; EQ-VAS, EuroQol-Visual Analogue Scale.
*$P < 0.05$.

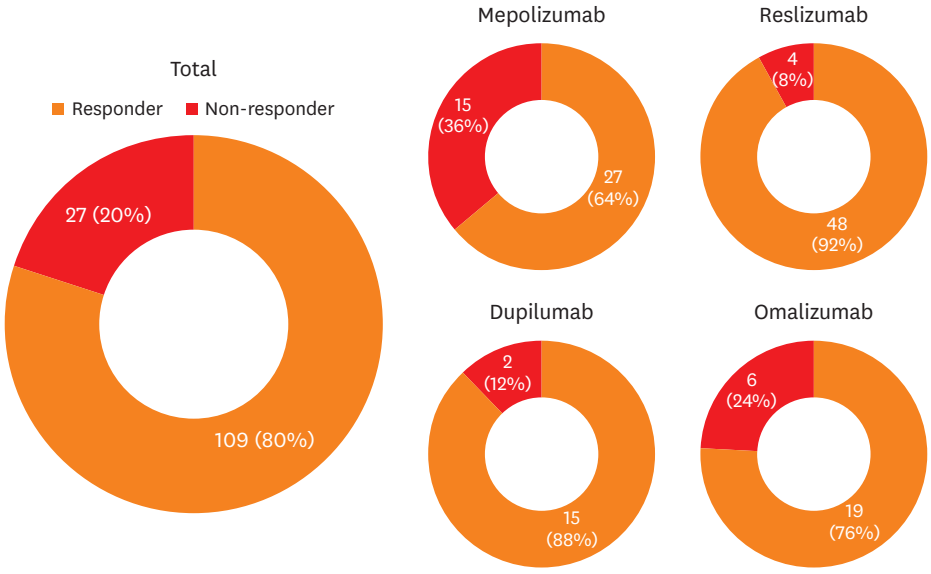

Fig. 6. Distribution of responders and non-responders in 4 biologic-treated groups. Evaluation was based on the GETE score, and 80% of patients were classified as responders.
GETE, Global Evaluation of Treatment Effectiveness.

17] vs. 41.3% [n = 45], $P = 0.036$). In addition, non-responders showed lower lung function, and a higher OCS maintenance dose than the responder groups (**Table 2**). We compared changes in acute exacerbations, pulmonary function, OCS maintenance dose, and ACT scores between the responder and non-responder groups following biologics administration. In the responder group, clinical indicators showed improvement (**Supplementary Fig. S1**).

https://doi.org/10.4168/aair.2024.16.3.253

Table 2. Comparison of baseline clinical characteristics between responders and non-responders

Characteristics	Total (n = 136)	Non-responder (n = 27)	Responder (n = 109)	*P* value
Age (yr)	52.7 ± 11.7	52.4 ± 10.8	52.8 ± 11.9	0.874
Female	75 (55.1)	14 (51.9)	61 (56.0)	0.701
BMI (kg/m^2)	24.9 ± 4.1	25.2 ± 3.6	24.8 ± 4.3	0.667
Smoking				0.614
Never smoker	74 (54.4)	13 (48.1)	61 (56.0)	
Ex-smoker	45 (33.1)	11 (40.7)	34 (31.2)	
Current smoker	7 (5.2)	1 (3.7)	6 (5.5)	
Asthma onset age (yr)	40.5 ± 14.7	44.4 ± 13.4	39.7 ± 14.9	0.197
Asthma control				0.175
Uncontrolled	40 (29.4)	8 (29.6)	32 (29.4)	
Partly controlled	49 (36.0)	6 (22.2)	43 (39.4)	
Controlled	19 (14.0)	6 (22.2)	13 (11.9)	
Asthma exacerbations over the past year, N	2.5 ± 3.5	1.8 ± 2.6	2.7 ± 3.7	0.457*
ACT score	16.8 ± 5.7	16.6 ± 4.2	16.8 ± 5.9	0.898
QLQAKA	56.7 ± 16	54 ± 11.5	57.1 ± 16.6	0.573
EQ-VAS	63.5 ± 21.1	67.8 ± 17.2	62.8 ± 21.7	0.515
Comorbidities				
Allergic rhinitis	101 (74.3)	18 (66.7)	83 (76.1)	0.298
Atopic dermatitis	18 (13.2)	2 (7.4)	16 (14.7)	0.382
Chronic rhinosinusitis	62 (45.6)	17 (63.0)	45 (41.3)	**0.036**
Nasal polyps	16 (11.8)	4 (14.8)	12 (11.0)	0.592
Pulmonary function test				
FEV1 (%)	67.6 ± 19	59.9 ± 18.5	69.6 ± 18.7	**0.020**
FEV1 (mL)	2,030.2 ± 767.3	1,765.4 ± 668.3	2,097.1 ± 779.1	**0.049**
FVC (%)	79.6 ± 14.2	74.3 ± 14.2	81 ± 14	**0.032**
FVC (mL)	3,019.5 ± 931.1	2,802.3 ± 843.3	3,074.3 ± 947.9	0.184
FEV1/FVC (%)	67.3 ± 13.8	63.9 ± 14.8	68.1 ± 13.4	0.161
FeNO (ppb)	61.1 ± 58.2	48.1 ± 32.1	63.8 ± 62	0.637*
Blood eosinophil (count)	610.7 ± 689	626.9 ± 655.8	606.9 ± 699.9	0.902*
Total IgE (IU/mL)	790.1 ± 825.8	406.3 ± 517.4	854 ± 856.1	0.126*
Medication				
Inhaled corticosteroids (mcg/day)†	888.9 ± 633.4	1,059.2 ± 730	846.8 ± 603.8	0.320*
OCS maintenance	38 (27.9)	14 (51.9)	24 (22.0)	**0.028**
OCS maintenance dose (mg/day)	2.8 ± 5	4.5 ± 5.7	2.4 ± 4.7	**0.010***

Continuous variables were presented as means ± standard deviations and categorical variables were presented as counts of events (%). The *P* values marked in bold indicate they are statistically significant. *P* values are calculated using nonparametric method (Wilcoxon rank sum test) or χ^2 test.
BMI, body mass index; ACT, Asthma Control Test; QLQAKA, Quality of Life Questionnaire for Adult Korean Asthmatics; EQ-VAS, EuroQol-Visual Analogue Scale; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; FeNO, fractional exhaled nitric oxide; OCS, oral corticosteroids.
*Nonparametric method (Wilcoxon rank sum test); †Budesonide equivalent dose.

Adverse reactions

No severe adverse events were reported during the study period. Adverse reactions were classified as mild and moderate, as described in **Supplementary Table S2**. The most common side effects were local rash and itching, which occurred in 4 cases.

DISCUSSION

This real-world study of patients with SA in Korea showed that add-on treatment with biologics significantly reduced the rate of acute exacerbation and the dose of OCS maintenance and improved lung function. Acute exacerbation can be further aggravated and can reduce the quality of life and increase medical costs; therefore, interventions to reduce acute exacerbations are important. For this reason, many studies evaluate the number

https://doi.org/10.4168/aair.2024.16.3.253

of exacerbations as an outcome.[24,25] There are some differences depending on the type of medication; however, the administration of biologics ≥ 4 months to Korean patients with SA reduced exacerbations by 92%. This is a greater reduction than that reported previous real-world studies.[13] The reduction in acute exacerbations observed in other similar real-world studies was approximately 60%–65%.[26-28] In addition, the efficacy of the biologics shown in the pivotal RCTs reduced acute exacerbation by around 40%–60%.[6-8,10,11] There are only a few studies with subgroup analysis results for only Korean patients in global RCTs. It has been shown that the efficacy of biologics in Koreans is much better.[29,30] The results of these studies, which analyzed Korean participants in the SIROCCO (benralizumab) and Liberty Asthma Quest (dupilumab) studies, showed that biologics treatment reduced acute exacerbations by 80% and 87%, respectively.[29,30]

Morbidity and mortality increase in long-term OCS users.[31,32] However, some patients require OCS as a maintenance regimen to control asthma. In addition, 20%–30% of Korean patients with SA belong to the OCS maintenance patient group.[33,34] In this study, we found that administration of biologics reduced OCS maintenance by 75%. The mean daily OCS maintenance dose in patients enrolled in the KoSAR study was 6.8 mg (prednisolone-equivalent dose) for OCS-dependent asthma,[34] which was higher than that in the present study. Before biologics were prescribed, the average OCS maintenance dose was 2.8 mg. This indirectly means that patients with more SA who may still need biologics are not receiving them. In Korea, the National Health Insurance (NHI) does not cover all kinds of biologics for asthma treatment. Therefore, the price influences the choice of biologics, and many patients cannot receive biologics even if they work well.

Lung function also improved in this study (220 mL based on FEV1), which was also higher than those in previous studies.[5,7,10] In the Korean subgroup analysis of the SIROCCO study, FEV1 improvement was significantly higher,[29] and the study also showed that lung function improved (360 mL). In addition, the quality of life was significantly improved owing to the improvement of these clinical parameters. No serious adverse reactions were experienced.

The results of this study, indicating a seemingly better drug response in the Korean cohort than others, may be attributed to the following reasons. Based on the results of previously conducted studies, drug indications were likely established according to predictions of favorable effects for each drug. Given the high cost of biologics, careful consideration would have been exercised in selecting patients based on these indications.

Most patients showed excellent effects when administered the T2 inflammation phenotype; however, some patients presented with a poor effect. In a real-world study of mepolizumab, non-responders were 27.3%, and had a high maintenance OCS dose and low comorbid proportion with nasal polyps.[35] In a real-world study of benralizumab, non-responders were 13.8%, and there was no significant difference in the clinical features between the responder and non-responder groups.[36] In our study, approximately 20% of patients had a poor response. These patients showed low pulmonary function, a high proportion and maintenance dose of OCS, and highly comorbid chronic rhinosinusitis.

To date, many real-world studies on the effects of biologic treatment have been published. However, this is a multi-center cohort study that evaluated the effects of all biologics, not focusing only on specific biologics. It is possible that the mechanisms of biologics may have influenced the clinical outcomes. This study also did not exclude patients with a history

https://doi.org/10.4168/aair.2024.16.3.253

of smoking. Furthermore, the value of this study lies in its ability to reflect the conditions associated with biologics administration in real-world settings, providing valuable insights for future policy-making and the management of SA. In this study, among the 25 patients who received omalizumab, 11 received the slight variations in the actual appropriate dosage according to the dosing table. However, 14 patients actually received a single vial (150 mg). Despite omalizumab being reimbursed in 2020 during the patient enrollment period for this study, many patients still could not receive the appropriate dosage treatment. This may be due to strict reimbursement conditions and financial constraints.

This study has several limitations. First, the number of patients for the comparison between each group was insufficient, and there was a limit to the comparison of the effectiveness of each biologic. In addition, this study is limited in evaluation effectiveness, as it does not directly compare the effects of drugs, such as in head-to-head study. Second, the comparative analysis of the effects was performed at 4 months, not at 6 or 12 months. This could be attributed to the cost of biologics, as patients are required to cover the expenses of the medications. Despite the highly favorable effects of biologics, many patients opt for more affordable corticosteroids or feel burdened by the prospect of long-term injections, even after the initiation of biologics. Furthermore, many patients discontinue biologics or extend the interval between administrations because of financial burdens. Lastly, there is no available information regarding benralizumab since it was the most recently approved biologic in Korea.

In conclusion, this study provides a real-world demonstration of the significant role of biologics in the treatment of SA in Korea. Given their high effectiveness in Koreans, biologics should be administered without restrictions to patients with SA with T2 inflammation. Therefore, large-scaled further studies focusing on cost-effectiveness are warranted.

ACKNOWLEDGMENTS

This work was supported by a grant of the Korea Health Technology R&D Project through the Korea Health Industry Development Institute (KHIDI), funded by the Ministry of Health & Welfare, Republic of Korea (grant number: HC19C0318). This research was supported by the Korea National Institute of Health research project (project No. 2022-ER1205-00). The authors thank the investigators, clinical research coordinators, and participants for their time and efforts in the Korean Severe Asthma Registry (KoSAR).

SUPPLEMENTARY MATERIALS

Supplementary Table S1
Biologics effectiveness in 4 biologic-treated group

Supplementary Table S2
Adverse reactions in 4 biologic-treated group

Supplementary Fig. S1
Change in clinical outcomes between responders and non-responders.

https://doi.org/10.4168/aair.2024.16.3.253

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