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Effect of biologic therapies on quality of life in severe asthma: Findings from the PRISM study

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ABSTRACT

Background: Anti-type 2 (T2) biologic therapies (biologics) improve exacerbation rates, lung function, and asthma-related quality of life (QoL) in patients with severe T2 asthma. However, studies comparing different biologics are lacking. We evaluated the QoL in patients with severe asthma comprehensively and compare the efficacy of different T2-directed biologics using QoL questionnaires.

Methods: We compared the QoL between severe and mild-to-moderate asthma and between severe asthma with and without biologics treatment. Data of mild-to-moderate were extracted from the Cohort for Reality and Evolution of Adult Asthma in Korea, and data of severe asthma were collected from the Precision Medicine Intervention in Severe Asthma. We included 183 patients with severe asthma treated with T2 biologics or conventional therapy between April 2020 and May 2021 and assessed QoL of them using the Questionnaire for Adult Korean Asthmatics (QLQAKA), Severe Asthma Questionnaire (SAQ), and EuroQoL-5Dimensions (EQ-5D) at baseline and 6 months.

Results: The EQ-5D index (0.803) of severe asthma was lower than that of other chronic diseases representing a worse QoL. The scores for all questions of QLQAKA, except "cough," were lower (less control) in the severe asthma group than in the mild-to-moderate asthma group at baseline and 6 months ($P < 0.05$). The total scores and subscores of all domains of the QLQAKA, SAQ, and EQ-5D improved significantly 6 months after biologic therapy but not after conventional therapy. The total QLQAKA, SAQ, and EQ-5D scores improved after 6 months in the anti-IL-5 ($P < 0.05$) and anti-IL-4/IL-13 ($P < 0.05$) treatment groups with no significant difference between groups ($P > 0.05$).

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Conclusion: QoL was worse in severe asthma than in mild-to-moderate asthma and other chronic diseases. T2 biologics equally improved QoL in patients with severe asthma.

Keywords: Severe asthma, Quality of life, Biologics, Anti-IL-5, Anti-IL-4/IL-13

INTRODUCTION

Asthma is a chronic inflammatory airway disease, characterized by reversible airway obstruction. It is one of the most common noncommunicable diseases with approximately 300 million asthma patients worldwide.[1] Uncontrolled asthma causes various respiratory symptoms, limits activity, increases the healthcare burden, and can result in the deterioration of quality of life (QoL). Therefore, asthma control is vital for maintaining an adequate QoL in patients with asthma.[2,3] In addition, QoL is associated with numerous factors, such as age, socioeconomic position, and different diseases,[4,5] and a multidimensional relationship exists between asthma and QoL.[3]

Asthma is classified into severe and a non-severe disease according to the degree of asthma control obtained with conventional therapy.[6] Most patients have non-severe asthma, which is well controlled with conventional anti-inflammatory treatment including inhaled corticosteroids and long-acting beta$_2$ agonists. Although patients with severe asthma account for approximately 5% of the asthma population,[7] they incur 50–80% of the total cost of asthma management.[8,9] Management of severe asthma remains a challenge; however, biologic therapies (biologics) have presented a new paradigm in severe asthma treatment. Biologics reduce exacerbations and improves asthma control and QoL in patients with severe asthma.[10]

However, most previous studies on the effectiveness of biologics focused on individual agents,[11–15] and comprehensive and/or comparative studies are lacking. Therefore, in this study, we aimed to assess the QoL of patients with severe asthma, and evaluate the overall efficacy of T2 biologics (anti-immunoglobulin [Ig] E, anti-interleukin [IL]-5, anti-IL-5R, and anti-IL-4/IL-13) in improving QoL. In addition, we compared the efficacy of QoL improvement between anti-IL-5 and anti-IL-4/IL-13 therapies.

METHODS

Study population

The Precision Medicine Intervention in Severe Asthma (PRISM) project has been underway since May 2020.[16] This multicenter, prospective, observational cohort study enrolled patients with severe asthma who visited severe asthma clinics in South Korea (38 centers) and the United Kingdom (3 centers).[16] This study included 183 adult patients with severe asthma, aged between 18 and 80 years, who commenced treatment with 1 of 5 different biologics (omalizumab, mepolizumab, reslizumab, benralizumab, or dupilumab) with conventional therapy or only conventional therapy at 22 severe asthma clinics in Korea between April 2020 and May 2021. Biologic therapy was considered for severe asthmatics with type 2 inflammation, who were inappropriately controlled despite of a high dose inhaled corticosteroids plus long-acting beta$_2$ agonists. This study was a real-world study, and physicians utlimately selected a biologic agent based on the inclusion criteria for the prescription of biologics in Korea[16] as well as ATS/ERS guideline for severe asthma and the Global Initiative for Asthma report. The patients who responded to the Questionnaire for Adult Korean Asthmatics (QLQAKA), Severe Asthma Questionnaire (SAQ), and EuroQoL-5Dimensions (EQ-5D) at baseline, and completed at least 6 months of follow up, were included in this study to assess the progress of the QoL at 6 months (Table 1). Biologic therapy was started after the baseline questionnaire survey, and continued for 6 months. The EQ-5D data from other chronic diseases and malignancies were also obtained from previously published reports.[17,18]

QLQAKA	SAQ	EQ-5D
1. Chest discomfort.	1. My social life.	1. Mobility
2. Feeling of asthmatic attack.	2. My personal life.	2. Self-care
3. Shortness of breath.	3. My leisure activities.	3. Usual activity
4. Smoke, excitative smell.	4. My jobs around the house.	4. Pain/discomfort
5. Wheeze.	5. My work or education.	5. Anxiety/ depression
6. Cough.	6. My family life - how it affects me.	
7. Emotional stress.	7. My family life - how it affects others.	
8. Nocturnal asthma.	8. Depression.	
9. Weather, public hazard.	9. Irritable.	
10. Jitter about treatment.	10. Anxiety in general.	
11. Sputum, foreign body sensation.	11. Worry that asthma may get worse.	
12. House dust, frowst.	12. Worry about long term side effects of medicines.	
13. Hard daily activities.	13. Getting tired.	
14. Light daily activities.	14. Problems at night.	
15. Social activities.	15. The way I look.	
16. Work or school activities.	16. Problems with food.	
17. All daily activities.		

Table 1. Items of the questionnaire for adult Korean asthmatics, severe asthma questionnaire and EuroQoL-5Dimensions

The Cohort for Reality and Evolution of adult Asthma in Korea (COREA) study is a prospective, observational multicenter, follow-up study involving Korean patients with asthma.[19] The QLQAKA data from 826 patients with mild-to-moderate asthma in the COREA cohort were also collected. Patients with mild-to-moderate asthma were identified by experts in the COREA study.

This study was approved by the Institutional Review Board of Inje University Haeundae Paik Hospital H (2020-05-002) and Asan Medical Center (2019–1676). All patients provided written informed consent.

Quality of life questionnaires

The QLQAKA was developed in 2000 specifically for adult Korean asthmatics based on their lifestyle.[20] It is divided into 4 domains, including environment (3 items: 4, 9, and 2), emotion (3 items: 2, 7, and 10), activity (5 items: 13, 14, 15, 16, and 17), and symptoms (6 items: 1, 3, 5, 6, 8, 11). Patients were asked to rate each item on a five-point response scale. The minimal clinically important difference (MCID) for the QLQAKA is 0.5.[20]

The Korean version of SAQ is a validated tool for assessing the health-related QoL of individuals with severe asthma.[21] The SAQ comprises 16 questions covering various facets of life and a general question evaluating the overall QoL. It encompasses 3 domains, including my life (7 items: 1–7), my mind (4 items: 8–11), and my body (5 items: 12–16) graded on a seven-point scale. In addition, a SAQ-global score is graded

on a single 100-point Borg-type scale. MCID for the SAQ is 0.5 and for the SAQ-global is 11.[22] A higher QLQAKA and SAQ score indicates better asthma control.

The EQ-5D is a commonly used tool that was developed in Europe to assess overall QoL,[23] and the Korean version of the EQ-5D has been validated.[24] It comprises 5 questions assessed on a three-point scale, where each question represents a separate domain, including mobility (EQ-5D 1), self-care (EQ-5D 2), usual activities (EQ-5D 3), pain/discomfort (EQ-5D 4) and anxiety/depression (EQ-5D 5). A reduction in an EQ-5D domain score represents an improvement in QoL. The EQ-5D index was calculated using the Korean valuation set.[25]

Statistical analyses

Demographic, clinical, and asthma characteristics were compared between the biologic and conventional treatment groups using the Student's t-test or Wilcoxon rank sum test for normally or non-normally distributed continuous variables and the chi-squared test or Fisher's exact test for categorical variables. Continuous variables are presented as mean and standard deviation, and categorical variables are presented as frequencies and percentages.

Before the analysis, we calculated the mean scores for the QLQAKA,[20] SAQ,[21] and EQ-5D[23] domains based on the definition provided by previous studies. The delta values of the QLQAKA, SAQ, and EQ-5D scores from baseline to 6 months were also obtained to facilitate comparison between conventional and biologic treatment, as well as between anti-IL-4/IL-13 and anti-IL-5. The Student's and paired Student's t-tests were used to compare the mean QoL score of each domain and standardized mean differences (Cohen's *d*) were calculated between the following 2 groups: biologics vs conventional therapies or baseline vs 6 months. A Cohen' *d* of 0.2 is considered small, 0.5 a medium, and 0.8 a large effect.[26] Pearson's correlation analysis was used to evaluate construct validity between the QLQAKA, SAQ and EQ-5D. All statistical analyses were performed using SAS (SAS Institute v.9.4, Cary, NC). A value of $P \leq 0.05$ was considered statistically significant, and significant *P*-values were adjusted by the Bonferroni method for multiple comparisons.

RESULTS

Comparison of quality of life among patients with chronic diseases in Korea

The overall EQ-5D index scores of patients with severe asthma in the PRISM study was compared with that of other chronic diseases (Fig. 1) obtained from previous studies.[17,18] The EQ-5D index score of severe asthma was the lowest (0.803), followed by the scores of arthritis (0.849),[17] malignancy (0.861),[18] asthma (0.873),[17] diabetes (0.898),[17] hypertension (0.900),[17]

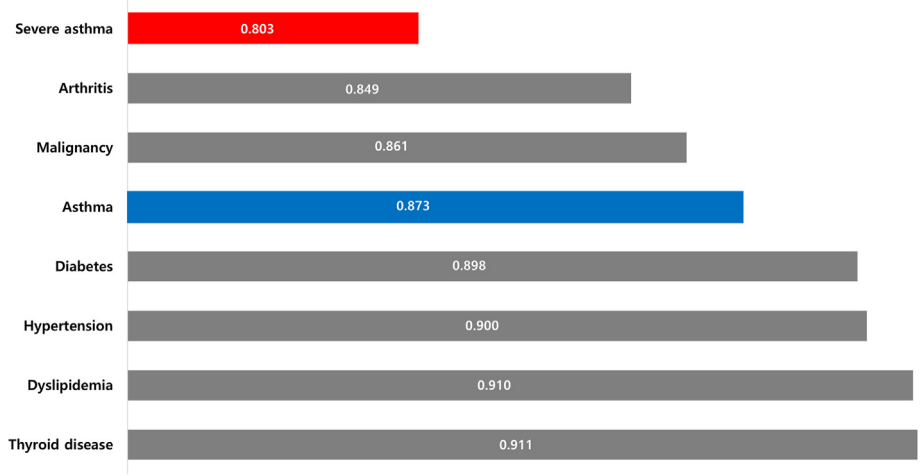

Fig. 1 Comparison of the EQ-5D index scores among patients with severe asthma and other chronic diseases. EQ-5D, EuroQoL-5Dimensions

dyslipidemia (0.910)[17] and thyroid disease (0.911).[17] The EQ-5D index scores of patients with asthma were not derived from the COREA cohort.

Comparison of quality of life between patients with severe and mild-to-moderate asthma

The QLQAKA score was assessed at baseline and after 6 months. For multiple comparison of the QLQAKA scores between patients with severe and mild-to-moderate asthma, significant *P*-values were adjusted by Holm-Bonferroni method. At baseline, the scores for all questions, except "cough", were significantly lower in the severe asthma group than in the mild-to-moderate asthma group ($P < 0.05$, Fig. 2a). The score for the "cough" did not differ significantly between the severe and mild-to-moderate groups (3.11 vs. 3.21, $P = 0.305$) (Fig. 2a). After 6 months, the scores for all 17 questions including "cough" were significantly lower in the severe asthma group than in the mild-to-moderate asthma group ($P < 0.05$; Fig. 2b). The scores on the "sputum, foreign body sensation" question were the lowest among all 17 questions in both the groups at baseline (severe asthma, 2.67; mild-to-moderate asthma, 3.07) and after 6 months (severe asthma, 3.31; mild-to-moderate asthma, 3.6) (Fig. 2).

Baseline clinical characteristics of patients with severe asthma and differences between the biologic and conventional treatment groups

The study included 183 patients with severe asthma, with a mean age of 53.61 ± 11.28 years (Table 2). The mean age at the time of asthma diagnosis was 42.20 ± 13.49 years. The complete demographic and clinical details of the overall cohort are provided in Table 2. During the study period, 44 patients continued conventional treatment without biologics, and 139 patients were treated with biologics. Dupilumab was the most commonly administered biologics (n = 54), followed by reslizumab (n = 40), mepolizumab (n = 30), omalizumab (n = 8), and benralizumab (n = 7).

Patients in the biologics treatment group were significantly younger than those in the conventional treatment group (52.06 ± 11.05 years vs 58.72 ± 10.73 years, $P = 0.001$) and were diagnosed with asthma at a younger age (40.26 ± 12.88 years vs 48.37 ± 13.80 years, $P = 0.001$) (Table 2). The frequency of unscheduled visits to the emergency department due to asthma

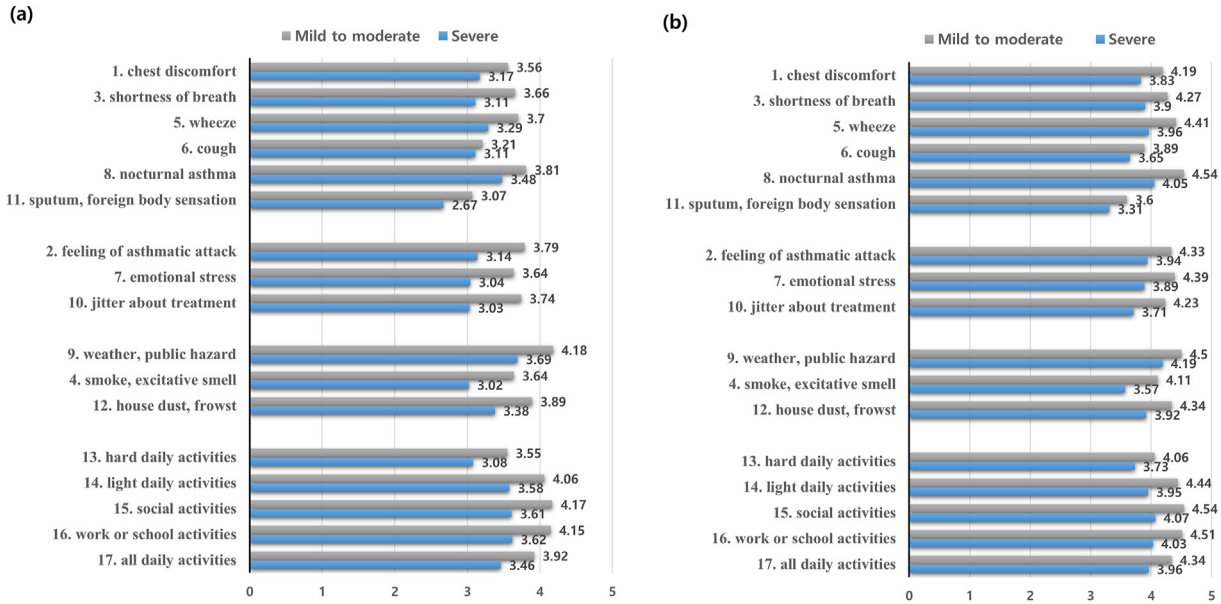

Fig. 2 Comparison of the QLQAKA scores between patients with mild-to-moderate and severe asthma at baseline (a) and 6 months (b). Significant *P*-values were adjusted by Holm-Bonferroni method for multiple comparisons. QLQAKA, Questionnaire for Adult Korean Asthmatics

	Total N = 183, (%)	Biologics N = 139, (%)	Conventional N = 44, (%)	*P*-value
Age, years	53.61 ± 11.28	52.06 ± 11.05	58.72 ± 10.73	0.001
Age at the time of symptom onset	40.65 ± 14.20	38.89 ± 13.68	46.23 ± 14.68	0.003
Age at the time of asthma diagnosis	42.20 ± 13.49	40.26 ± 12.88	48.37 ± 13.80	0.001
Duration of asthma*, months	11.35 ± 8.39	11.68 ± 8.63	10.35 ± 7.69	0.366
Sex, male	84 (45.9)	64 (46.0)	20 (46.5)	0.957
Body mass index, kg/m^2	24.70 ± 4.06	24.93 ± 3.60	24.48 ± 4.21	0.497
Oral corticosteroids maintenance	58 (31.7)	51 (36.7)	7 (16.3)	0.012
Current smoker	15 (8.2)	10 (7.2)	5 (11.6)	0.355
Number of AEs in the last 1 year	4.37 ± 10.60	4.55 ± 9.12	3.77 ± 14.50	0.672
History of AEs in the last 1 year	98 (53.6)	80 (57.6)	18 (41.9)	0.071
Unscheduled OPD visit	49 (26.8)	41 (29.5)	8 (18.6)	0.159
Unscheduled ED visit	31 (16.9)	28 (20.1)	3 (7.0)	0.045
Hospitalization	27 (14.8)	22 (15.8)	5 (11.6)	0.498
Intensive care unit admission	2 (1.1)	1 (0.7)	1 (2.3)	0.278
Allergic rhinitis	129 (70.5)	102 (73.4)	26 (60.5)	0.105
Chronic rhinosinusitis	78 (42.6)	68 (48.9)	10 (23.3)	0.003
Atopy	86 (47.0)	72 (51.8)	13 (30.2)	0.004
Whole blood cells, × 10^3 cells/μL	8.00 ± 2.50	8.18 ± 2.54	7.4 ± 2.32	0.072
Blood eosinophils, cells/μL	600.36 ± 543.37	676.35 ± 563.93	354.72 ± 382.88	<0.0001
Serum total IgE, kU/L	425.28 ± 516.90	463.54 ± 561.89	291.35 ± 284.12	0.067
Sputum neutrophils, %	53.60 ± 33.74	53.78 ± 33.98	53.09 ± 33.53	0.917
Sputum eosinophils, %	21.10 ± 28.11	22.75 ± 28.35	16.37 ± 27.23	0.249
Fractional exhaled nitric oxide, ppb	64.65 ± 52.53	69.21 ± 52.81	49.61 ± 49.25	0.036
Prebronchodilator FEV_1, %	62.75 ± 19.61	61.68 ± 19.35	66.19 ± 20.25	0.189
Prebronchodilator FEV_1/FVC	0.65 ± 0.15	0.64 ± 0.15	0.67 ± 0.17	0.247
Asthma Control Test	15.88 ± 5.23	15.27 ± 5.20	17.86 ± 4.87	0.004
Sino-Nasal Outcome Test-22	41.22 ± 24.67	43.13 ± 24.53	34.95 ± 24.36	0.060

Table 2. Baseline clinical characteristics of the study patients *Values are presented as means ± standard deviations or numbers (%). AE, asthma exacerbation; BMI, body mass index; ED, emergency department; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 s; Ig E, immunoglobulin E; OPD, out-patient department.*

exacerbation in the past year was significantly greater in the biologics treatment group than in the conventional treatment group (20.1% vs. 7.0%, $P = 0.045$). Furthermore, the proportion of patients on maintenance oral corticosteroids (OCS) was significantly higher in the biologics treatment group than in the conventional treatment group (36.7% vs 16.3%, $P = 0.012$). The proportion of patients with atopy (51.8% vs. 30.2%, $P = 0.004$) and chronic rhinosinusitis (CRS) (48.9% vs 23.3%, $P = 0.003$) was significantly higher in the biologics treatment

group than in the conventional treatment group (Table 2). Blood eosinophil (676.35 ± 563.93 cells/uL vs 354.72 ± 382.88 cells/uL, $P < 0.001$) and fractional exhaled nitric oxide (FeNO) levels (69.21 ± 52.81 ppb vs 49.61 ± 49.25 ppb, $P = 0.036$) were significantly higher in the biologics treatment group than in the conventional treatment group. Lung function did not differ significantly between the 2wo groups (Table 2).

Comparison of quality of life between the biologic and conventional treatment groups

At baseline, the total score (53.32 vs 62.36, $P < 0.001$) and subscales in symptom (18.17 vs 20.93, $P < 0.001$), activity (16.69 vs 19.45, $P < 0.001$), and emotion (8.69 vs 10.85, $P < 0.001$) of QLQAKA were significantly lower in the biologics treatment group than in the conventional treatment group after adjusting significant *P*-values using Holm-Bonferroni methods (Supplementary Table S1). Effect sizes (Cohen's d) in total scores of the QLQAKA, SAQ and EQ-5D were 0.87, 0.49 and 0.51, respectively. Overall, the data indicated that, at baseline, patients in the biologics treatment group had worse asthma control and QoL than those of patients in the conventional treatment group. After 6 months of treatment, no significant differences in the total scores and all subscales for the QLQAKA were observed between the 2 groups (Supplementary Table S2). Total scores of the QLQAKA, SAQ and EQ-5D showed small effect size with lower than 0.5 between the 2 groups. My mind (22.27 ± 5.52 vs 19.28 ± 6.83, $P < 0.001$, Cohen's $d = 0.68$) subscale of SAQ in the biologics treatment group were significantly higher than in the conventional treatment group.

Fig. 3 depicts the detailed changes in the 3 QoL questionnaire domains from baseline to 6 months. In the biologics treatment group, all scores of 17 questions of the QLQAKA (Figs. 3a) and 16 questions of the SAQ (Fig. 3b) increased after 6 months of treatment. In contrast, the scores on 6 items ("cough," "nocturnal asthma," "hard daily activities," "light daily activities," "social activities," and "work or school activities") of the QLQAKA (Figs. 3a) and 12 of 14 items (the exceptions were "social life" and "family life-how it affects

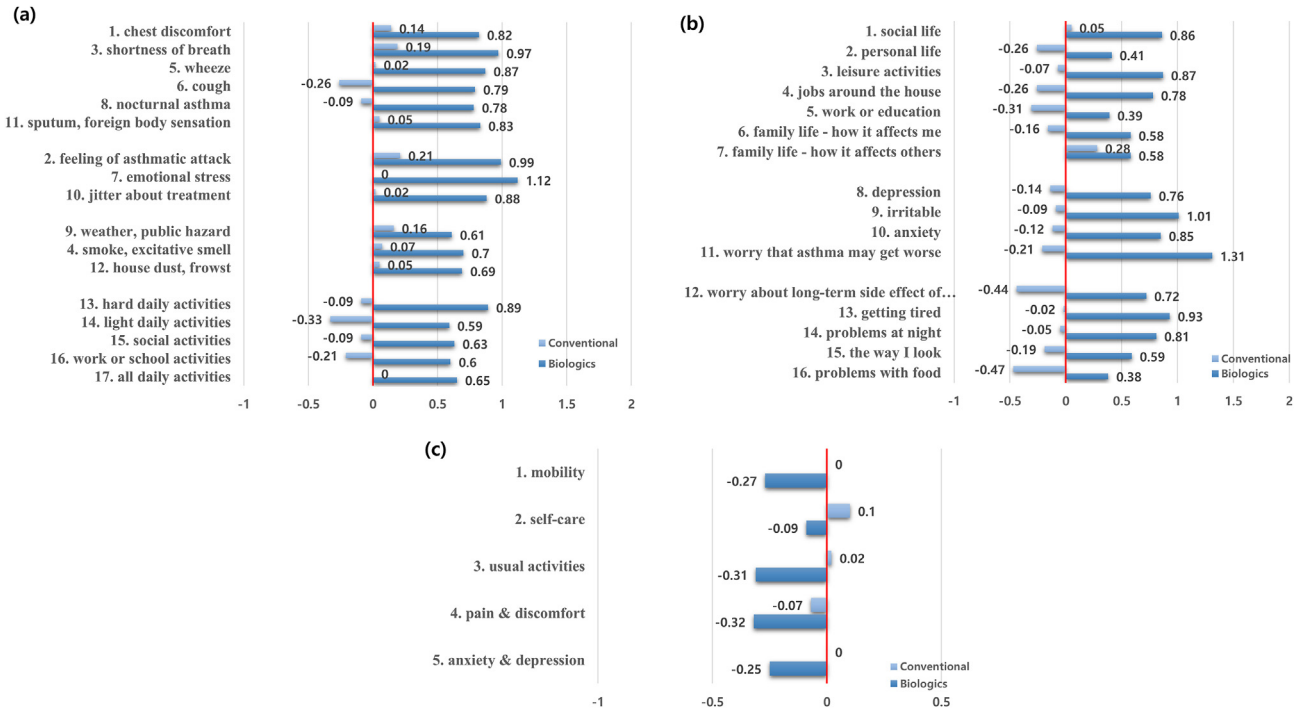

Fig. 3 Changes in the QLQAKA (a), SAQ (b), and EQ-5D (c) scores from baseline to 6 months of treatment in patients with severe asthma according to conventional and biologics treatment. EQ-5D, EuroQoL-5Dimensions; SAQ, Severe Asthma Questionnaire; QLQAKA, Questionnaire for Adult Korean Asthmatics

others") of the SAQ (Fig. 3b) decreased in the conventional treatment group.

In the EQ-5D survey, the scores of all 5 items decreased in the biologics treatment group, whereas the scores of 2 items ("self-care" and "unusual activities") increased in the conventional treatment group (Fig. 3c). In the biologics treatment group, the highest changing scores were for the following questions: "emotional stress" (1.12 points) in the QLQAKA, "worry that asthma may get worse" (1.31 points) in the SAQ, and "pain and discomfort" (−0.32 points) in the EQ-5D questionnaires (Fig. 3).

The total scores and subscales in all domains of the QLQAKA, SAQ and EQ-5D improved significantly after 6 months of biologics treatment (Supplementary Table S3). The differences in QLQAKA and SAQ total scores from baseline to 6 months were 13.16 and 11.78, respectively, which far exceeded the each MCID (0.5) in the biologics treatment group. There were medium and larger effect sizes in total scores and subscales in all domains of 3 questionnaires, and QLQAKA had the largest effect size among the 3 questionnaires. In contrast, the QLQAKA, SAQ and EQ-5D scores did not change significantly in the conventional therapy group after 6 months of treatment (Supplementary Table S4). The change in QLQAKA total score (0.34) during the study period was not significant compared to the MCID (0.5), and the difference in SAQ total score (−1.42) was much lower than the MCID (0.5) in the conventional treatment group, suggesting a worsening of asthma control.

Correlations between the Questionnaire for Adult Korean Asthmatics, Severe Asthma Questionnaire, and EuroQoL-5Dimensions

Items of the QLQAKA, SAQ and EQ-5D were shown in Supplementary Table 1. QLQAKA-activity, SAQ-my life, and EQ-5D-self-care & usual activity included overlapped items. QLQAKA-emotion, SAQ-my mind, and EQ-5D-anxiety/depression also had related items. Correlation analyses of these overlapping domains between QLQAKA, SAQ and EQ-5D in the biologics treatment group is shown in Supplementary Table S5. Overlapping domains of all 3 questionnaires were significantly correlated with each other ($P < 0.0001$) at baseline and 6 months. Changes of subscales in overlapping domains after treatment between the 3 questionnaires were also significantly correlated with each other ($P < 0.05$).

Subgroup analysis according to the type of biologics: anti-IL-5 and anti-IL-4/IL-13

In total, 70 patients who were treated with reslizumab or mepolizumab were allocated to the anti-IL-5 group, and 54 patients who were treated with dupilumab were allocated to the anti-IL-4/IL-13 group (Supplementary Table S6). No significant differences in age (51.34 ± 11.20 years vs 53.93 ± 9.88 years, $P = 0.176$) and sex (men: 41.4% vs 57.4%, $P = 0.078$) were observed between the anti-IL-5 and anti-IL-4/IL-13 groups. The duration of asthma was significantly shorter (9.96 ± 7.64 months vs 13.96 ± 9.42 months, $P = 0.013$) and the proportion of patients on maintenance OCS was lower (27.1% vs. 48.2%, $P = 0.016$) in the anti-IL-5 group than in the anti-IL-4/IL-13 group. The anti-IL-5 group had significantly higher blood eosinophils (829.22 ± 607.93 cells/μL vs 510.58 ± 483.87, $P = 0.002$) and FeNO levels (77.44 ± 54.39 ppb vs 53.75 ± 44.85 ppb, $P = 0.012$) and lower total serum IgE levels (312.65 ± 261.36 vs 567.00 ± 506.21, $P = 0.020$) than those of the anti-IL-4/IL-13 group.

The total scores and subscales in all domains of the QLQAKA, SAQ (Fig. 4a) and EQ-5D (Fig. 4b) improved significantly after 6 months of anti-IL-5 treatment. Similar improvements were observed across all QoL measures (QLQAKA, SAQ and EQ-5D) (Fig. 4c and d) in the anti-IL-4/IL-13 group after 6 months. There were no significant differences in the change in all scores of the QLQAKA, SAQ and EQ-5D between the 2 biologics treatment groups ($P > 0.05$; Fig. 5).

DISCUSSION

The present study demonstrated that T2 biologics could significantly improve the asthma-related QoL scores in patients with severe T2 asthma after 6 months in real-world clinical practice. All domains of QoL measures were improved with the use of biologics. Moreover, anti-IL-5 therapy (combined mepolizumab and reslizumab) resulted in similar improvements in QoL as that

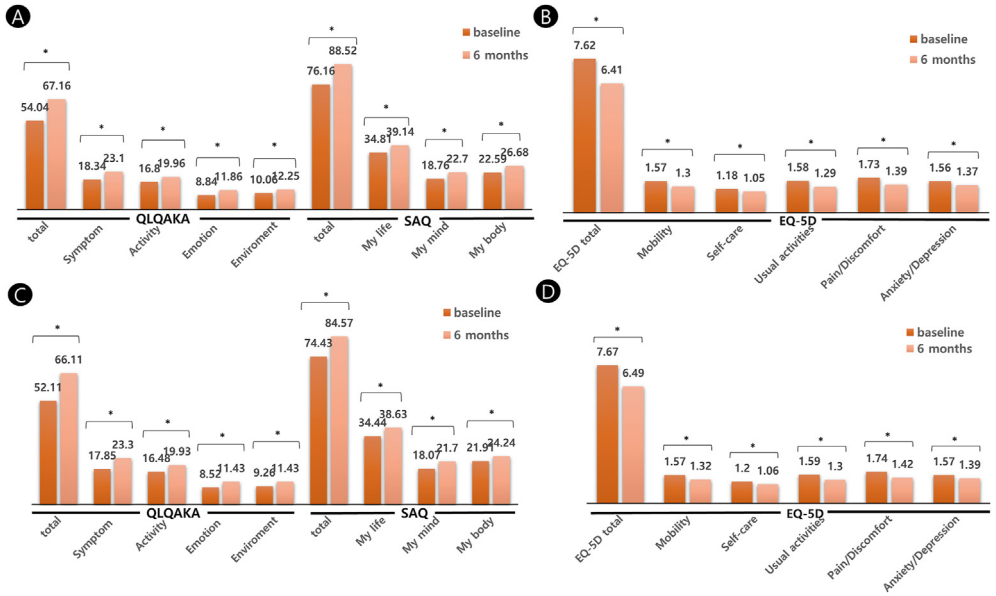

Fig. 4 Comparison of the quality of life of the patients from baseline to 6 months based on the type of biologics: QLQAKA/SAQ (a) and EQ-5D (b) of the anti-IL5 group; QLQAKA/SAQ (c) and EQ-5D (d) of the anti-IL-4/IL-13 group. Significant *P*-values were adjusted by Holm-Bonferroni method. *$P <$ adjusted significant *P*-value. EQ-5D, EuroQoL-5Dimensions; QLQAKA, Questionnaire for Adult Korean Asthmatics; SAQ, Severe Asthma Questionnaire

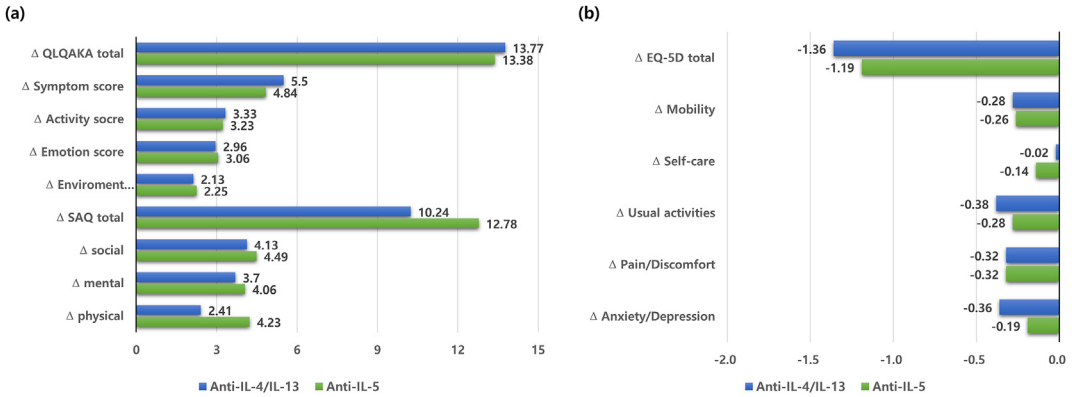

Fig. 5 Changes in the QLQAKA/SAQ (a), and EQ-5D (b) scores from baseline to 6 months based on the type of biologics. The *P*-values for all items were greater than adjusted significant *P*-values by Holm-Bonferroni method. EQ-5D, EuroQoL-5Dimensions; QLQAKA, Questionnaire for Adult Korean Asthmatics; SAQ, Severe Asthma Questionnaire

observed with dupilumab. In contrast, no improvement in QoL was observed using conventional treatment alone; indeed, the scores of most items in the 3 questionnaires indicated worsening in QoL scores. Therefore, the QoL of patients with severe asthma not treated with biologics or inappropriately controlled may gradually worsen over time.

Chronic diseases generally follow an irreversible and progressive course, with a significant disease burden. The prevalence of chronic diseases has risen, particularly in the aging population, and interest in the QoL of these patients has been growing.[27,28] Patients with stroke, chronic obstructive pulmonary disease, and ischemic disease of the lower extremities have a lower QoL than that of patients with other common chronic diseases.[29,30] Interestingly, a previous study using the Korean National Health and Nutrition Examination Survey data reported that the EQ-5D index scores of patients with arthritis were the lowest and those of patients with asthma was the second lowest compared with those of

patients with thyroid diseases, dyslipidemia, and hypertension.[17] In the present study, the QoL of patients with severe asthma was lower than in previous reports of patients with other chronic diseases,[17] and worse than that of Korean patients with cancer.[18] The reduced QoL in patients with severe asthma was more profound than that observed in other chronic diseases, emphasizing the importance in asthma therapy.

Severe asthma does not respond well to conventional treatment and its disease burden is substantially higher than that of non-severe asthma.[8,9] The QoL of patients with asthma is associated with the status of asthma control and severity.[31,32] In the present study, a reduction in QoL was observed across asthma symptoms, activity, emotion, and environment domains of the QLQAKA in severe asthma compared to non-severe asthma, which persisted over 6 months of treatment. Therefore, more effective therapeutic measures are required to improve QoL in patients with severe asthma.

However, the "cough" score in the QLQAKA was similar between patients with severe and non-severe asthma, indicating the importance of cough in QoL measures across all types of asthma. The "sputum and foreign body sensation" score was the lowest among all 17 questions at baseline and 6 months. This indicates that cough, sputum, and foreign body sensation may not respond well to treatment compared to other symptoms, such as wheezing and shortness of breath. Cough, sputum, and foreign body sensation are manifested in various conditions, such as allergic rhinitis, CRS, gastroesophageal reflux disease, tonsillitis, pharyngitis, thyroid disease, and anxiety, as well as asthma, but their etiologies and pathophysiology remain unclear.[33–35] Therefore, physicians should manage these comorbidities to improve the asthma-related QoL. Further studies are needed to determine the mechanisms underlying refractory symptoms, such as cough, sputum, and foreign body sensation, in severe asthma.

Biologics are powerful adjuvant therapies in severe asthma that reduce the rate of exacerbation and requirement for OCS, as well as improve asthma control and QoL.[10–15] However, comparative studies on the efficacy of biologics are lacking.[11–15] A recent meta-analysis of the comparative efficacy of biologics (anti-IL-4, anti-IL-5 and anti-IL-13) reported that both anti-IL-5 and anti-IL-4 therapies significantly improved the Asthma Quality of Life Questionnaire scores.[36] In the present study, both anti-IL-5 and anti-IL-4/IL-13 therapies significantly improved the QoL of patients with severe asthma to a similar degree. Patients in the anti-IL-4/IL-13 group exhibited higher levels of total serum IgE, longer asthma duration, and greater frequency of maintenance OCS use than those of patients in the anti-IL-5 group. In contrast, blood eosinophil and FeNO levels were higher in the anti-IL-5 group than in the anti-IL-4/IL-13 group. Although the anti-IL-5 and anti-IL-4/IL-13 groups seemed to have a relatively high proportion of patients with late-onset eosinophilic asthma and allergic asthma, respectively, no difference in QoL improvement was observed between them. This indicates that anti-IL-5 and anti-IL-4/IL-13 have similar efficacy with respect to improvements in QoL.

Biologics treatment resulted in the greatest change in the scores for emotional stress, concerns about asthma exacerbation, and discomfort in daily activities in the 3 questionnaires used in the present study. Psychological distress is associated with the status of asthma control, and the prevalence of anxiety and depression increases in severe asthma.[37,38] According to a study including 90 patients with severe asthma, treatment with biologics (benralizumab, mepolizumab, omalizumab) led to significant improvements in psychological distress, anxiety, and depression.[39] A recent study involving 82 patients with severe asthma reported that biologics therapy (benralizumab, mepolizumab, dupilumab, omalizumab) had psychological benefits to patients with severe asthma and that a history of depression was predictive of a lower response to biologics.[40] Thus biologics may have a significant ameliorative effect on the psychological burden in patients with severe asthma. Further research is needed to explore the interaction between psychological conditions and severe asthma and the management of mental health in patients with severe asthma.

Numerous factors affect QoL in patients with asthma as well as the status of asthma control; advanced age, lower education level, and lack of physical activity are associated with a poor QoL.[41–

[43] In the present study, baseline QoL in the biologics treatment group was worse than that of conventional treatment group, although the mean age of patients in the biologics treatment group was significantly lower. This could be attributed to the poor status of asthma control (higher proportion of patients on maintenance OCS and more frequent emergency room visits) in the biologics treatment group than in the conventional therapy group. The presence of CRS significantly diminishes the QoL,[44] and CRS was more common in the biologics treatment group than in the conventional treatment group. However, no significant difference in the Sino-Nasal Outcome Test-22 was observed between the 2 groups, and the impact of CRS on QoL may have been limited in our study. Furthermore, no significant differences in the history of exacerbation and current-smoker status were observed between the 2 groups.

Patients in the biologics treatment group exhibited more prominent eosinophilic/T2 inflammation (higher level of blood eosinophils and FeNO) than that of patients in the conventional treatment group. The effect of the different immunologic mechanisms underlying asthma on QoL measures is unknown; however, these effects may be indirect, influencing disease control and airway inflammation.

The present study had some limitations. First, data on non-severe and severe asthma were extracted from the COREA and PRISM cohorts, respectively. However, most patients from the PRISM cohort were also included in the COREA cohort, and the collection methods for demographic and clinical data were similar in both cohorts. Second, there are many different ways to evaluate QoL, but no optimal method has been established. Discrepancies may exist between generic and disease-specific health related QoL measures.[45,46] Therefore, 3 types of QoL questionnaires were used to ensure comprehensive evaluation of QoL in the present study. Generic health-related QoL was evaluated by the EQ-5D questionnaire, allowing indirect comparison severe asthma with other chronic diseases. The SAQ evaluated QoL in severe asthma, and the QLQAKA to measure QoL in severe asthma in the Korean population. The data from the 4 questionnaires were consistent, and there were significant correlations of overlapping domains between the 3 questionnaires, supporting the significance of the results in the present study. In addition, when comparing the QoL between in the biologics and conventional treatment groups, or assessing the change of QoL from baseline to 6 months of biologics treatment, QLQAKA showed the largest effect size, indicating that it may be the most sensitive tool assessing QoL compared to SAQ and EQ-5D. Third, asthma severity or control status was more severe in the biologics than in the conventional treatment group. Improving effect of QoL in the biologics treatment group might be somewhat overestimated, as in regression to the mean. Finally, the number of patients who were administered omalizumab and benralizumab was relatively small, and patients who were administered tezepelumab were not included in the present study. Long-term large-scale real-world studies are warranted to overcome these limitations.

In conclusion, the QoL of patients with asthma was lower than that of several other chronic diseases and that of patients with severe asthma was even lower. Conventional treatment demonstrated limitations in improving the QoL of patients with severe asthma, whereas T2-directed biologics had a significant impact on QoL in real-world practice. In particular, the psychological burden of patients with severe asthma was relieved by biologic therapies, necessitating further studies to investigate this effect. No significant differences in the benefits on the asthma-related QoL scores were observed between anti-IL-5 and anti-IL-4/IL-13 therapies.

Abbreviations

COREA, Cohort for Reality and Evolution of Adult Asthma in Korea; CRS, chronic rhinosinusitis; EQ-5D, EuroQoL-5Dimensions; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; Ig, immunoglobulin; IL, interleukin; PRISM, Precision Medicine Intervention in Severe Asthma; QLQAKA, Questionnaire for Adult Korean Asthmatics; QOL, quality of life; SAQ, Severe Asthma Questionnaire.

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Availability of data and materials
The data-sets analyzed during the current study are available from the corresponding author on reasonable request.

Author contributions
TK designed the study; HR, SL, SK, JK, HP, HP, SK, JC, SK, SP, SK, JM, JJ, YC, CP, BK, JK, MY, MK, YN, TL, BL, and TK collected the data; HR and HK analyzed the data; HR, HK, and TK interpreted the data; HR drafted the manuscript; TK, IA, and KFC revised the manuscript; all authors critically reviewed and approved the manuscript.

Ethics approval
This study was approved by the Institutional Review Board of Inje University Haeundae Paik Hospital (2020-05-002) and Asan Medical Center (2019–1676). All patients provided written informed consent.

Authors' consent for publication
All authors agreed to the publication of this work in the World Allergy Organization Journal.

Declaration of competing interest
The authors declare that they have no relevant conflicts of interest.

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Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2024.100957.

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