Shim et al. World Allergy Organization Journal (2023) 16:100848
http://doi.org/10.1016/j.waojou.2023.100848

WORLD ALLERGY ORGANIZATION JOURNAL

Open Access

A comparison of treatment response to biologics in asthma-COPD overlap and pure asthma: Findings from the PRISM study

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ABSTRACT

Background: Despite the increasing use of biologics in severe asthma, there is limited research on their use in asthma-chronic obstructive pulmonary disease overlap (ACO). We compared real-world treatment responses to biologics in ACO and asthma.

Methods: We conducted a multicenter, retrospective, cohort study using data from the Precision Medicine Intervention in Severe Asthma (PRISM). ACO was defined as post-bronchodilator forced expiratory volume in 1 s (FEV1)/forced vital capacity (FVC) <0.7 and a smoking history of >10 pack-years. Physicians selected biologics (omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab) based on each United States Food & Drug Administration (FDA) approval criteria.

Results: After six-month treatment with biologics, both patients with ACO ($N = 13$) and asthma ($N = 81$) showed positive responses in FEV1 (10.69 ± 17.17 vs. 11.25 ± 12.87 %, $P = 0.652$), Asthma Control Test score (3.33 ± 5.47 vs. 5.39 ± 5.42, $P = 0.290$), oral corticosteroid use (-117.50 ± 94.38 vs. -115.06 ± 456.85 mg, $P = 0.688$), fractional exhaled nitric oxide levels (-18.62 ± 24.68 vs. -14.66 ± 45.35 ppb, $P = 0.415$), sputum eosinophils (-3.40 ± 10.60 vs. -14.48 ± 24.01 %, $P = 0.065$), blood eosinophils (-36.47 ± 517.02 vs. -363.22 ± 1294.59, $P = 0.013$), and exacerbation frequency (-3.07 ± 4.42 vs. -3.19 ± 5.11, $P = 0.943$). The odds ratio for exacerbation and time-to-first exacerbation showed no significant difference after full adjustments, and subgroup analysis according to biologic type was also showed similar results.

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http://doi.org/10.1016/j.waojou.2023.100848
Received 19 July 2023; Received in revised from 23 October 2023; Accepted 12 November 2023
Online publication date 12 December 2023

Conclusions: Biologics treatment response patterns in patients with ACO and asthma were comparable, suggesting that biologics should be actively considered for ACO patients as well.

Keywords: Asthma-COPD overlap, Asthma, Biologics, Monoclonal antibodies, Treatment response

INTRODUCTION

Asthma-chronic obstructive pulmonary disease (COPD) overlap (ACO) does not refer to a single disease entity.[1] It is a heterogeneous condition that shares some features of both asthma and COPD, which are chronic inflammatory airway diseases.[2] Clinical features of ACO include asthma with fixed airflow obstruction, eosinophilic COPD, COPD with a significant bronchodilator response, and smoking asthmatics.[3,4] ACO is reported to have worse clinical outcomes and higher mortality rates than either asthma or COPD alone, but its pathophysiology remains unclear, and there is no effective and specific treatment for ACO.[2] The current uncertainty regarding ACO primarily results from the lack of consensus about its definition or diagnostic criteria, which would enable a more standardized approach to diagnosis and management.[1]

In 2014, the Global Initiative for Asthma (GINA) and the Global Initiative for Chronic Obstructive Lung Disease (GOLD) issued a joint statement describing ACO as a condition with features of both asthma and COPD, with persistent airflow limitation.[5] The diagnostic criteria for ACO vary depending on whether it is approached from the asthma or COPD perspective.[1,6] A definition of ACO derived from COPD cohorts typically includes a diagnosis of COPD with a post-bronchodilator (BD) forced expiratory volume in 1 s/forced vital capacity (FEV1/FVC) < 0.7 and a history of asthma before the age of 40 years, or a great BD response of $\geq$15 % in FEV1.[1,7] However, in asthma cohorts, a definition of ACO was proposed based on a diagnosis of asthma with a significant smoking history, plus a post-BD FEV1/FVC <0.7.[8] The lack of a standardized definition also makes it difficult to compare outcomes across studies on ACO.

Importantly, most clinical trials for drug development have only enrolled patients with pure asthma or pure COPD, excluding those with suspected ACO, resulting in limited research on the treatment of ACO. Although precision medicine and biologics have been highlighted in recent years for asthma, ACO has been left behind in this regard. Therefore, real-world studies on the use of biologics in ACO are important. This study aimed to generate new evidence on the use of biologics in patients with ACO by comparing clinical outcomes, including inflammatory markers, lung function, symptom control, and exacerbation rates, between patients with asthma and ACO undergoing treatment with biologics for 6 months or more, using multicenter, real-world adult severe asthma cohort data from Korea.

METHODS

Study population

The Precision Medicine Intervention in Severe Asthma (PRISM) project is a prospective, observational, multicenter cohort study involving patients with severe asthma attending asthma clinics in Korea (38 centers) and the United Kingdom (3 centers), which has been conducted since May 2020.[9] This study enrolled adult patients between 18 and 80 years who were diagnosed with asthma by allergy or pulmonology experts and were classified as having severe asthma according to the European Respiratory Society/American Thoracic Society (ERS/ATS) criteria published in 2014.[10] Accordingly, patients required GINA Step 4–5 treatment or systemic corticosteroids for more than 50 % of the past year or were still uncontrolled despite these treatments.[10]

Subsequently, the subjects were classified into type 2 (T2)-high or T2-low asthma based on skin prick tests, blood eosinophils, induced sputum

eosinophils, and fractional exhaled nitric oxide (FeNO) levels. T2-high asthma was defined as meeting 1 or more of the following criteria: blood eosinophils ≥150/μL, sputum eosinophils ≥2 %, FeNO levels ≥20 ppb, and suspected allergic asthma with sensitivity to inhalant allergen.[9,11] Patients with T2-high asthma were newly treated with biologics such as omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab according to United States Food and Drug Administration (FDA) approval criteria or continued with conventional treatment according to the usual clinical protocols. Follow-up evaluations were performed at baseline, 1 month, 6 months, and 12 months.

From the PRISM database, we selected only Korean biologic users aged ≥40 years who completed at least 6 months of follow-up. Biologics were administered on the day of enrollment after screening, in accordance with the recommended dose and treatment interval protocols specific to each pharmaceutical agent using FDA-approved criteria, which are applied to patient care in Korea. This study was approved by the Institutional Review Board of Ewha Womans University Medical Center (SEUMC 2020-04-014-023) and Asan Medical Center (2019–1676).

Variable definitions

ACO was defined as asthma with post-BD airway flow limitation (FEV1/FVC <0.7) and smoking history of ≥10 pack-years (Fig. 1).[12] A total of 94 subjects were enrolled, including 13 patients with ACO and 81 with pure asthma. Baseline clinical and laboratory characteristics were obtained at enrollment, and pulmonary function, blood and sputum eosinophils, FeNO levels, and asthma control test (ACT) were measured at every follow-up visit. A bronchodilator reversibility test was performed after stopping short-acting β2-agonist ≥4 h and LABA ≥24 h, and positive BD response was defined as the increase in FEV1 of >12 % and >200 mL from baseline after 10–15 min of inhalation of salbutamol 200–400 μg.[11] Atopy was identified as positive for inhalant allergens by skin prick test or multiple allergen simultaneous test (MAST). Asthma exacerbation was defined as positive if subjects experienced at least 1 of the following: an unscheduled outpatient visit, an emergency room (ER) visit, hospitalization, or corticosteroid burst, identified through monthly telephone surveys. Corticosteroid burst was defined as the use of a prednisolone dose greater than 30 mg/day or its equivalent for more than 3 consecutive days.

Statistical analyses

Descriptive statistics are presented as number (%) for categorical variables or a mean ± standard deviation for continuous variables. Demographic, clinical, and asthma characteristics were assessed between the pure asthma and the ACO groups using the Student's *t*-test or Wilcoxon rank sum test for normally or non-normally distributed continuous variables and the Chi-square test or Fisher's exact test for categorical variables. A univariate and multivariate logistic regression model was used to identify the association between the presence of asthma exacerbation and ACO among study groups. Adjusting variables to identify potential confounders included age, sex, body mass index, smoking pack-year, blood eosinophils (cells/μL), and FeNO (ppb) levels at baseline. To model time-to-first exacerbation, the Kaplan-Meier time-to-event analysis was plotted in the ACO and pure asthma groups. A *P*-value <0.05 was considered statistically significant. All statistical analyses were performed with SAS (SAS Institute v. 9.4, Cary, NC) and R version 4.0.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

General characteristics

A total of 94 patients with severe asthma treated with biologics were enrolled, of which 81 had pure asthma and 13 had ACO. Patient baseline characteristics are presented in Table 1. There were more males in the ACO group than in the pure asthma group (100 % vs 44.4 %, P < 0.001) and mean smoking pack-year was 29.6 ± 16.1 and 12.6 ± 14.9, in the ACO group and pure asthma group, respectively (P = 0.001). Patients with ACO exhibited lower blood eosinophil counts (453.3 ± 304.5 vs 730.9 ± 588.3/μL, P = 0.015) and less atopy (18.2 % vs 65.5 %, P = 0.007) than patients with pure asthma, and lower post-BD FEV1 (47.8 ± 18.8 vs. 67.6 ± 19.0 %, P = 0.001) and

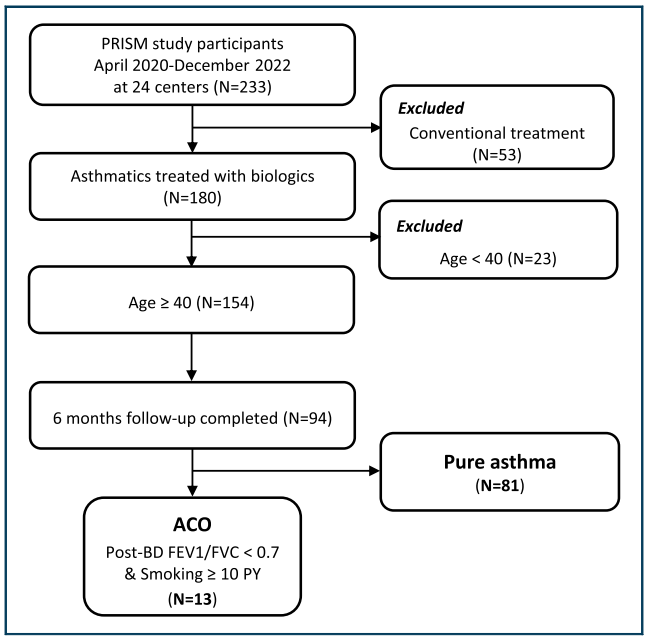

Fig. 1 Study population flow chart. Abbreviations: ACO, asthma-chronic obstructive pulmonary disease overlap; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; PY, pack-year.

FEV1/FVC ratio (0.50 ± 0.13 vs 0.68 ± 0.12, P < 0.001). Patients with ACO had a higher budesonide equivalent inhaled corticosteroid (ICS) dose than patients with pure asthma (1027.7 ± 626.4 vs 685.5 ± 467.5 mcg/day, P = 0.023).

Clinical characteristics according to biologic therapy

There was no difference in asthma medications between the ACO and pure asthma groups except for the use of biologics. Among the biologics used, dupilumab was more frequently used in the ACO group (61.5 % vs 23.5 %, P = 0.009), while omalizumab and benralizumab were not used in the ACO group (Table 2). The selection of biologics was at the discretion of the treating physician according to guidelines and each drug's FDA approval criteria, without any intervention. When examining the baseline characteristics according to the biologic agents used, patients with ACO treated with reslizumab had a lower post-BD FEV1/FVC ratio (0.53 ± 0.12 vs 0.70 ± 0.10, P = 0.038) and a higher smoking pack-year (32.3 ± 15.7 vs 10.0 ± 10.6, P = 0.042) than pure asthmatics treated with reslizumab, and patients with ACO treated with dupilumab had lower pre-BD FEV1/FVC ratio (0.50 ± 0.17 vs 0.65 ± 0.14, P = 0.037), post-BD FEV1/FVC ratio (0.47 ± 0.15 vs 0.68 ± 0.13, P = 0.012), and a higher smoking pack-year (31.1 ± 18.3 vs 14.9 ± 17.8, P = 0.019) than pure asthmatics treated with dupilumab. There were no significant differences in blood and sputum eosinophils, serum IgE, comorbidities, or other factors between the groups (Table 3). When comparing anti-interleukin (IL)-5 agents, mepolizumab and reslizumab, with dupilumab, the ACO group had lower pre- and post-BD FEV1/FVC ratios and a higher smoking pack-year compared to the pure asthma group (Supplement Table 1).

Changes in lung function and other parameters in ACO and pure asthma after treatment with biologics for 6 months

We examined changes in FEV1 (mL and % predicted), FEV1/FVC ratio, ACT score, budesonide equivalent ICS dose, prednisolone equivalent oral corticosteroid (OCS) dose, FeNO, blood eosinophil count, sputum eosinophil, and the number of exacerbations before the start of biologic treatment and 6 months later. Both the ACO and asthma groups showed positive responses with no significant difference in FEV1 improvement (10.7 ± 17.2 vs 11.3 ± 12.9 %, P = 0.652), ACT score increase (3.3 ± 5.5 vs 5.4 ± 5.4, P = 0.290), reduction in ICS dose (−66.7 ± 460.0 vs −17.9 ± 236.2 mcg/day, P = 0.912), reduction in OCS maintenance dose (−117.5 ± 94.4 vs −115.1 ± 456.9 mg, P = 0.688), reduction in FeNO levels (−18.6 ± 24.7 vs. −14.7 ± 45.4 ppb, P = 0.415), reduction in sputum eosinophils (−3.4 ± 10.6 vs −14.5 ± 24.0 %, P = 0.065), and decrease in exacerbation frequency (−0.96 ± 2.47 vs −1.40 ± 2.63, P = 0.575). The only significant difference observed was a decrease in blood eosinophil levels (−36.5 ± 517.0 vs −363.2 ± 1294.6/μL, P = 0.013) (Table 4). No significant differences were observed when comparing the 2 groups for each biologic (Supplement Table 2).

Comparison of exacerbation risk between ACO and pure asthma

There was no significant difference in the risk of asthma exacerbation between the ACO and pure asthma groups during the six-to-nine-month follow-up period. This finding remained consistent across various adjusted models (Table 5).

Characteristics	ACO (n = 13)	Pure asthma (n = 81)	P-value
Male, n (%)	13 (100)	36 (44.4)	<.0001
Age (years)	54.5 ± 9.3	54.1 ± 9.0	0.886
BMI (kg/m^2)	25.3 ± 3.2	24.9 ± 3.3	0.669
Onset of asthma (age)	44.2 ± 12.1	42.6 ± 11.9	0.663
Duration of asthma (years)	10.7 ± 5.8	11.3 ± 8.5	0.791
Smoking status, n (%)			0.001
Nonsmoker	0	45 (55.6)	
Past smoker	12 (92.3)	31 (38.3)	
Current smoker	1 (7.7)	5 (6.2)	
Smoking history (pack-years)	29.6 ± 16.1	12.6 ± 14.9	0.001
Comorbidities, n (%)			
Allergic rhinitis	8 (61.5)	63 (77.8)	0.295
Chronic rhinosinusitis	5 (38.5)	44 (54.3)	0.374
Nasal polyp	2 (15.4)	19 (23.5)	0.726
NERD	0	2 (2.5)	1.000
Atopic dermatitis	3 (23.1)	10 (12.4)	0.381
Bronchiectasis	0	3 (3.7)	1.000
Obstructive sleep apnea	1 (7.7)	3 (3.7)	0.454
Gastroesophageal reflux disease	6 (46.2)	21 (25.9)	0.186
Diabetes mellitus	2 (15.4)	9 (11.1)	0.646
Hypertension	4 (30.8)	27 (33.3)	1.000
Family history of allergic disease, n (%)	9 (69.2)	57 (70.4)	1.000
Laboratory findings			
WBC (10^3/μL) (n = 94)	8.7 ± 2.5	8.1 ± 2.5	0.444
Blood eosinophil (%) (n = 94)	5.6 ± 3.9	9.5 ± 6.9	0.007
Blood eosinophil (/μL) (n = 94)	453.3 ± 304.5	730.9 ± 588.3	0.015
C-reactive protein (mg/dL) (n = 67)	0.4 ± 0.4	0.4 ± 0.7	0.836
Serum total IgE (IU/mL) (n = 72)	838.0 ± 834.5	439.2 ± 593.9	0.078
Sputum eosinophil (%) (n = 66)	12.3 ± 23.8	24.3 ± 30.8	0.228
Sputum neutrophil (%) (n = 62)	54.7 ± 39.7	48.6 ± 34.9	0.605
Sputum eosinophil ≥2 % (n = 66)	6 (54.6)	36 (65.5)	0.511
Atopy (n = 90)	2 (18.2)	50 (63.3)	0.007
FeNO (ppb) (n = 91)	48.7 ± 38.5	77.9 ± 49.6	0.046
FeNO ≥ 20 ppb	11 (84.6)	72 (92.3)	0.320
Lung function test			
Pre-bronchodilator FEV1 (%) (n = 94)	49.1 ± 21.4	63.4 ± 18.6	0.013
Pre-bronchodilator FEV1 (L) (n = 94)	1.78 ± 0.80	1.91 ± 0.72	0.567
Pre-bronchodilator FVC (%) (n = 94)	70.5 ± 19.2	75.3 ± 15.1	0.316
Pre-bronchodilator FVC (L) (n = 94)	3.3 ± 1.0	2.9 ± 1.0	0.119
Pre-bronchodilator FEV1/FVC (n = 94)	0.52 ± 0.14	0.66 ± 0.13	<.0001
Post-bronchodilator FEV1 (%) (n = 88)	47.8 ± 18.8	67.6 ± 19.0	0.001
Post-bronchodilator FEV1 (L) (n = 88)	1.73 ± 0.68	2.04 ± 0.70	0.154
Post-bronchodilator FVC (%) (n = 88)	71.6 ± 16.7	77.8 ± 16.0	0.164

(continued)

Characteristics	ACO (n = 13)	Pure asthma (n = 81)	P-value
Post-bronchodilator FVC (L) (n = 88)	3.4 ± 0.9	3.0 ± 0.9	0.215
Post-bronchodilator FEV1/FVC (n = 88)	0.50 ± 0.13	0.68 ± 0.12	<.0001
Positive bronchodilator response (n, %)	1 (7.69)	16 (19.75)	0.225
Budesonide equivalent ICS dose (mcg/day)	1027.7 ± 626.4	685.5 ± 467.5	0.023
Prednisolone equivalent OCS dose during last month (mg)	269.0 ± 138.0	223.3 ± 236.0	0.681
Annual exacerbation rate			
Ever experienced AE (previous 12 months), n (%)	10 (76.9)	50 (61.7)	0.364
All AE (/year)	4.2 ± 4.3	3.6 ± 5.2	0.663
SCS burst use, n (%)	6 (46.2)	37 (45.7)	1.000
ER visit (/year)	1.5 ± 0.6	1.7 ± 1.2	0.707
Unexpected outpatient visits (/year)	3.3 ± 3.4	2.5 ± 2.8	0.545
Hospitalization (/year)	1.3 ± 0.5	1.8 ± 0.8	0.225
ACT scores (total 25)	16.3 ± 4.2	15.2 ± 5.6	0.504

Table 1. (Continued) Characteristics of study participants (N = 94). *Data are presented as number (%) or mean ± standard deviation. P-value was calculated by Fisher's exact test for categorical variables and the t-test for continuous variables. Abbreviations: ACO, Asthma-COPD Overlap; BMI, body mass index; NERD, NSAID exacerbated respiratory disease; WBC, white blood cell; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; OCS, oral corticosteroids; AE, acute exacerbation; SCS, systemic corticosteroids; ER, emergency room; ACT, Asthma Control Test.*

When grouping by anti-IL5/R vs. dupilumab, there was also no difference in the risk of exacerbation between the ACO and pure asthma groups for each medication group in the all adjusted models (Table 6). Additionally, the time-to-first asthma exacerbation (TFE) analysis using Kaplan-Meier curves did not reveal any significant differences between the ACO and pure asthma groups (Fig. 2).

DISCUSSION

In this study, we compared treatment responses to biologics for 6 months between patients with ACO and pure asthma, with the selection of biologics determined according to the treating physician's discretion based on the guidelines and the FDA approval criteria for asthma in a real-world practice. Both the ACO and pure asthma groups exhibited positive treatment responses, including improvements in FEV1, ACT scores; reductions in ICS/OCS doses, FeNO levels, blood and sputum eosinophil counts, and exacerbation frequency. The only significant difference observed was a further reduction in blood eosinophil count in the pure asthma group compared to the ACO group. Furthermore, when adjusting for multiple confounding factors, there was no significant difference in the risk of exacerbation between the ACO and pure asthma groups treated with biologics. Additionally, the analysis of time-to-first asthma exacerbation using the Kaplan-Meier method revealed no significant difference between the ACO and pure asthma groups. Therefore, our study demonstrates that patients with ACO exhibit similar treatment response patterns to patients with pure asthma undergoing biologic therapy, as indicated by various treatment outcome measures.

The lack of a standardized definition or diagnostic criteria for ACO is problematic. ACO is generally referred to as a condition of persistent airflow limitation with clinical features that are consistent with both asthma and COPD.[13,14] Various definitions of ACO have been proposed, including conceptual definitions, combinations of major and minor criteria, and definitions from the perspective of COPD or asthma, respectively.[1,7,15] Therefore, there are inevitable obstacles when conducting research or extrapolating conclusions from previous ACO study results, as different studies use different ACO definitions based on

	ACO (n = 13)	Pure asthma (n = 81)	P-value
ICS[a]-LABA[b] only	3 (23.1)	26 (32.1)	0.748
ICS-LABA-LAMA[c]	10 (76.9)	54 (66.7)	0.540
Theophylline/aminophylline/doxofylline	5 (38.5)	26 (32.1)	0.753
Leukotriene receptor antagonist	9 (69.2)	58 (71.6)	1.000
Daily low dose OCS[d]	5 (38.5)	26 (32.1)	0.753
Omalizumab	0	4 (4.9)	1.000
Mepolizumab	2 (15.4)	23 (28.4)	0.502
Reslizumab	3 (23.1)	32 (39.5)	0.359
Dupilumab	8 (61.5)	19 (23.5)	0.009
Benralizumab	0	3 (3.7)	1.000

Table 2. The use of asthma medications in ACO and pure asthma groups (N = 94). *Data are expressed as number (%). P-value was calculated by Fisher's exact test for categorical variables. Abbreviations: ACO, Asthma-COPD Overlap; ICS, inhaled corticosteroid; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid. [a]Beclomethasone, budesonide, triamcinolone, ciclesonide, fluticasone, or flunisolide. [b]Salmeterol, formoterol, indacaterol, or vilanterol. [c]Tiotropium, aclidinium, glycopyrronium, or umeclidinium. [d]Methylprednisolone, prednisolone, hydrocortisone, dexamethasone, or deflazacort.*

different patient populations. Variable ACO prevalence rates are reported: 0.9–11 % in the general population, 11.1–61 % in patients with asthma, and 4.2–66 % in patients with COPD.[16] A meta-analysis of 19 asthma studies reported a pooled prevalence of ACO of 26.5 % (CI 19.5–33.6 %).[17] The use of different diagnostic criteria can result in significantly different prevalence rates. The prevalence of ACO was 3.0 % in 1067 patients with COPD using the ATS definition, 12.9 % using GINA/GOLD criteria, and 20.7 % based on the Spanish criteria.[18,19]

ACO is characterized by more severe symptoms, a lower quality of life, and more frequent exacerbations than asthma or COPD alone, resulting in higher medical costs.[20] However, despite the burden of ACO, there are limited treatment options available, as there is a lack of a standard definition for ACO, and there are no effective biomarkers or standard treatments.

In the era of precision medicine and the increasing use of biologics for severe asthma, there is still limited research on ACO. Currently, the biomarkers used in asthma, such as blood eosinophils, serum IgE, aeroallergen sensitization, and FeNO, are also used in ACO.[21,22] These biomarkers may help differentiate ACO among patients with COPD or choose biologics for uncontrolled ACO.[21,22] However, patients with uncontrolled ACO are approximately 3 times less likely to receive biologic therapy than those with asthma.[23] Therefore, biologic treatment in ACO is an area of research need and interest.

A post hoc analysis of the PROSPERO study to evaluate omalizumab effectiveness in ACO, which included 737 patients with ACO treated with omalizumab for 48 weeks, showed similar improvement in asthma symptom scores and exacerbation rates in ACO and asthma groups.[24] This study used the same definition of ACO as in our study, which is post-BD FEV1/FVC <0.70 and at least 10 pack-years of smoking.[24] The Australian Xolair Registry reported symptom control and quality of life improvement in 177 patients with ACO treated with omalizumab, while no significant improvement in lung function compared to asthma alone was observed.[25] Another study on the effect of omalizumab in patients with asthma with or without fixed airway obstruction found that both groups showed improvement in exacerbation rates, but only the non-fixed airway obstruction group showed slight improvement in FEV1.[26]

	Mepolizumab (n = 25)		P-value	Reslizumab (n = 35)		P-value	Dupilumab (n = 27)		P-value
	ACO (n = 2)	Pure asthma (n = 23)		ACO (n = 3)	Pure asthma (n = 32)		ACO (n = 8)	Pure asthma (n = 19)	
Male, n (%)	2 (100)	6 (26.1)	0.093	3 (100)	16 (50)	0.234	8 (100)	13 (68.4)	0.136
Age (years)	50.5 ± 9.2	52.7 ± 8.6	0.882	57.3 ± 15.4	54.9 ± 9.5	0.907	54.4 ± 7.7	53.2 ± 9.8	0.563
BMI (kg/m^2)	25.3 ± 4.9	24.5 ± 3.7	0.729	25.4 ± 4.5	24.7 ± 3.0	0.726	25.3 ± 2.8	25.9 ± 3.2	0.773
Onset of asthma (age)	43.5 ± 13.4	40.2 ± 12.7	0.787	47.0 ± 32.5	44.6 ± 12.8	0.971	43.6 ± 7.2	39.4 ± 9.8	0.213
Duration of asthma (years)	7.0 ± 4.2	11.7 ± 8.8	0.518	14.0 ± 12.7	10.3 ± 6.9	0.611	10.8 ± 4.6	13.8 ± 10.8	0.674
Smoking status, n (%)			0.050			0.093			0.234
Nonsmoker	0	19 (82.6)		0	16 (50)		0	4 (21.1)	
Past smoker	2 (100)	4 (17.4)		2 (66.7)	13 (40.6)		8 (100)	13 (68.4)	
Current smoker	0	0		1 (33.3)	3 (9.4)		0	2 (10.5)	
Smoking history (pack-years)	19.5 ± 5.0	14.9 ± 22.3	0.518	32.3 ± 15.7	10.0 ± 10.6	0.042	31.1 ± 18.3	14.9 ± 17.8	0.019
Comorbidities, n (%)									
Allergic rhinitis	1 (50)	22 (95.6)	0.157	2 (66.7)	21 (65.6)	1.000	5 (62.5)	15 (79.0)	0.633
Chronic rhinosinusitis	1 (50)	13 (56.5)	1.000	1 (33.3)	19 (59.4)	0.565	3 (37.5)	10 (52.6)	0.678
Nasal polyp	2 (100)	6 (26.1)	0.093	0	6 (18.8)	1.000	0	6 (31.6)	0.136
NERD	0	1 (4.4)	1.000	0	0	N/A	0	1 (5.3)	1.000
Atopic dermatitis	0	4 (17.4)	1.000	1 (33.3)	3 (9.4)	0.313	2 (25.0)	1 (5.3)	0.201
Laboratory findings									
WBC (10^3/μL)	6.6 ± 0.1	8.6 ± 2.4	0.222	7.4 ± 2.8	7.7 ± 1.7	0.726	9.7 ± 2.3	8.7 ± 3.7	0.196
Blood eosinophil (%)	11.7 ± 2.1	12.1 ± 8.2	0.804	8.2 ± 1.5	9.8 ± 6.7	0.770	3.1 ± 2.1	5.2 ± 3.8	0.204

Blood eosinophil (/μL)	773.7 ± 156.6	990.1 ± 698.6	0.961	629.0 ± 324.8	752.5 ± 605.1	0.977	307.4 ± 241.7	368.0 ± 207.6	0.335
Serum total IgE (IU/mL)	N/A	325.1 ± 329.6	N/A	1422.5 ± 1265.0	387.4 ± 500.3	0.116	671.0 ± 717.9	374.7 ± 352.3	0.677
Sputum eosinophil (%)	35	30.8 ± 30.1	1.000	3.7 ± 3.2	13.6 ± 26.8	0.823	13.4 ± 29.2	32.8 ± 37.5	0.235
Sputum neutrophil (%)	53	45.5 ± 31.3	0.776	39.0 ± 49.0	60.7 ± 36.2	0.521	61.7 ± 40.5	34.8 ± 35.9	0.117
Atopy	0	13 (56.5)	0.100	1 (33.3)	17 (53.1)	0.603	1 (12.5)	16 (84.2)	0.001
FeNO (ppb)	104.5 ± 84.2	85.6 ± 52.1	0.757	33.7 ± 9.1	70.6 ± 45.3	0.235	40.4 ± 21.0	70.6 ± 48.4	0.108
Lung function test									
Pre-bronchodilator FEV1 (%) v(n = 23)	57.5 ± 7.8	57.4 ± 16.1	0.843	49.0 ± 25.2	66.7 ± 19.1	0.258	47.0 ± 23.8	65.0 ± 20.9	0.106
Pre-bronchodilator FEV1 (L) (n = 23)	2.36 ± 0.40	1.68 ± 0.63	0.159	1.61 ± 0.65	2.00 ± 0.73	0.466	1.70 ± 0.92	2.12 ± 0.83	0.264
Pre-bronchodilator FVC (%) (n = 23)	81.0 ± 11.3	72.3 ± 15.3	0.553	64.0 ± 20.5	77.3 ± 15.0	0.258	70.4 ± 21.0	77.1 ± 15.7	0.464
Pre-bronchodilator FVC (L) (n = 23)	4.2 ± 0.4	2.6 ± 0.9	0.063	2.9 ± 0.7	3.0 ± 1.0	1.000	3.3 ± 1.0	3.2 ± 0.9	0.733
Pre-bronchodilator FEV1/FVC (n = 23)	0.56 ± 0.04	0.65 ± 0.16	0.326	0.54 ± 0.13	0.67 ± 0.10	0.096	0.50 ± 0.17	0.65 ± 0.14	0.037
Post-bronchodilator FEV1/FVC (n = 21)	0.53 ± 0.06	0.63 ± 0.12	0.203	0.53 ± 0.12	0.70 ± 0.10	0.038	0.47 ± 0.15	0.68 ± 0.13	0.012
Budesonide equivalent	1200.0 ± 339.4	864.4 ± 543.8	0.274	1200.0 ± 1131.4	678.0 ± 499.3	0.595	910.0 ± 656.8	545.6 ± 243.1	0.218

(continued)

	Mepolizumab (n = 25)		P-value	Reslizumab (n = 35)		P-value	Dupilumab (n = 27)		P-value
	ACO (n = 2)	Pure asthma (n = 23)		ACO (n = 3)	Pure asthma (n = 32)		ACO (n = 8)	Pure asthma (n = 19)	
ICS dose (mcg/day)									
Prednisolone equivalent OCS dose during last month (mg)	70	462.2 ± 443.5	0.349	N/A	148.1 ± 98.4	N/A	318.8 ± 94.4	244.4 ± 229.6	0.411
OCS maintenance, n (%)	1 (50)	4 (17.4)	0.367	0	12 (37.5)	0.536	4 (50)	8 (42.1)	1.000
Annual exacerbation rate (/year)									
Ever experienced AE (previous 12 months), n (%)	2 (100)	16 (69.6)	1.000	3 (100)	18 (56.3)	0.259	5 (62.5)	12 (63.2)	1.000
All AE (/year)	5.5 ± 0.7	4.0 ± 5.4	0.275	2.3 ± 1.5	3.1 ± 4.0	0.808	4.6 ± 5.3	4.2 ± 7.3	0.644
SCS burst use, n (%)	2 (100)	11 (47.8)	0.523	2 (66.7)	14 (43.8)	0.582	2 (25)	9 (47.4)	0.405
ER visit (/year)	N/A	1.8 ± 1.0	N/A	2	1.9 ± 1.5	0.647	1.3 ± 0.6	1.7 ± 1.2	1.000
Unexpected outpatient visits (/year)	3	3.0 ± 2.0	0.847	1	1.5 ± 0.7	0.590	4.0 ± 4.1	3.8 ± 5.5	0.668
ACT scores (total 25)	14.5 ± 9.2	15.5 ± 5.8	0.766	14.3 ± 2.1	14.8 ± 5.4	0.977	17.7 ± 3.4	15.6 ± 6.2	0.476

Table 3. Baseline characteristics according to biologics type in ACO vs pure asthma groups (N = 87). *Data are presented as number (%) or mean ± standard deviation. P-value was calculated by the Wilcoxon rank sum test for continuous variables. Abbreviations: ACO, Asthma-COPD Overlap; BMI, body mass index; NERD, NSAID exacerbated respiratory disease; WBC, white blood cell; IgE, immunoglobulin E; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroids; OCS, oral corticosteroids; AE, acute exacerbation; SCS, systemic corticosteroids; ER, emergency room; ACT, Asthma Control Test.*

Variables	ACO (n = 13)	Pure asthma (n = 81)	P-value
ΔFEV1 (L)	0.38 ± 0.67 (n = 13)	0.32 ± 0.42 (n = 81)	0.649
ΔFEV1 (%)	10.7 ± 17.2 (n = 13)	11.3 ± 12.9 (n = 81)	0.652
ΔFEV1/FVC	0.03 ± 0.06 (n = 13)	0.03 ± 0.09 (n = 80)	0.959
ΔACT	3.3 ± 5.5 (n = 13)	5.4 ± 5.4 (n = 79)	0.290
ΔBudesonide equivalent ICS dose (mcg/day)	−66.7 ± 460.0 (n = 13)	−17.9 ± 236.2 (n = 75)	0.912
ΔPrednisolone equivalent OCS maintenance dose (mg)	−117.5 ± 94.4 (n = 4)	−115.1 ± 456.9 (n = 7)	0.415
ΔFeNO (ppb)	−18.6 ± 24.7 (n = 13)	−14.7 ± 45.4 (n = 77)	0.688
ΔBlood eosinophil (/μL)	−36.5 ± 517.0 (n = 13)	−363.2 ± 1294.6 (n = 78)	0.013
ΔSputum eosinophil (%)	−3.4 ± 10.6 (n = 5)	−14.5 ± 24.0 (n = 31)	0.065
ΔNumber of exacerbation	−0.96 ± 2.47	−1.40 ± 2.63	0.575

Table 4. The changes in treatment response parameters in the ACO and pure asthma group after 6 months of treatment with biologics. *The changes (Δ) were calculated by 6 M − baseline. P-value was calculated by the Wilcoxon rank sum test for continuous variables. Abbreviations: ACO, Asthma-COPD Overlap; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ACT, Asthma Control Test; ICS, inhaled corticosteroids; OCS, oral corticosteroids; FeNO, fractional exhaled nitric oxide.*

Adjusted model	Reference	All exacerbations			SCS burst			Unexpected outpatient visit		
	Pure asthma	ACO		p-value	ACO		p-value	ACO		p-value
		OR	95 % CI		OR	95 % CI		OR	95 % CI	
Model 1: no adjustment	1.0	2.4	0.7, 8.1	0.176	2.3	0.6, 8.7	0.210	2.8	0.6, 16.0	0.257
Model 2: age, sex, BMI adjusted	1.0	2.7	0.7, 11.0	0.168	2.2	0.5, 9.9	0.289	8.2	0.6, 111.3	0.113
Model 3: age, sex, BMI + smoking pack-year	1.0	2.1	0.5, 10.3	0.342	1.4	0.3, 7.4	0.689	7.6	0.4, 129.9	0.164
Model 4: Model 3 + blood eosinophils	1.0	2.2	0.5, 10.5	0.335	1.4	0.3, 7.4	0.689	10.8	0.5, 254.1	0.139
Model 5: Model 3 + FeNO	1.0	2.4	0.5, 11.9	0.303	1.8	0.3, 9.9	0.524	7.1	0.4, 131.1	0.188
Model 6: Model 3 + blood eosinophils, FeNO	1.0	2.3	0.5, 11.8	0.303	1.8	0.3, 9.9	0.524	7.3	0.4, 141.9	0.191

Table 5. Risk of asthma exacerbation in the ACO and pure asthma group (N = 94). *All adjusting variables were measured at baseline visit. Abbreviations: ACO, Asthma-COPD Overlap; OR, odds ratio; CI, confidence interval; SCS, systemic corticosteroid; BMI, body mass index; FeNO, fractional exhaled nitric oxide.*

Adjusted model	Reference	Mepolizumab & Reslizumab (n = 60)			Dupilumab (n = 27)		
	Pure asthma	ACO		p-value	ACO		p-value
		OR	95 % CI		OR	95 % CI	
Model 1: no adjustment	1.0	0.8	0.1, 7.9	0.854	5.3	0.8, 34.1	0.077
Model 2: age, sex, BMI adjusted	1.0	1.1	0.1, 13.1	0.919	3.5	0.5, 26.4	0.231
Model 3: age, sex, BMI + smoking pack-year	1.0	0.9	0.1, 13.6	0.924	1.6	0.1, 18.8	0.716
Model 4: Model 3 + blood eosinophils	1.0	0.9	0.1, 13.5	0.917	1.4	0.1, 17.1	0.806
Model 5: Model 3 + FeNO	1.0	1.1	0.1, 17.3	0.958	2.1	0.1, 33.6	0.615
Model 6: Model 3 + blood eosinophils, FeNO	1.0	1.1	0.1, 17.7	0.948	1.6	0.1, 27.7	0.765
Model 7: Model 3 + blood eosinophils, FeNO, number of exacerbations at baseline	1.0	0.9	0.1, 15.4	0.931	2.2	0.1, 50.1	0.634

Table 6. Risk of asthma exacerbation in ACO and pure asthma group according to biologics type (N = 87). *All adjusting variables were measured at baseline visit. Abbreviations: ACO, Asthma-COPD Overlap; OR, odds ratio; CI, confidence interval; BMI, body mass index; FeNO, fractional exhaled nitric oxide.*

A study using Medicare data reported that mepolizumab treatment reduced exacerbation rates and OCS use over a 12-month follow-up period in patients with both severe asthma and COPD diagnosis.[27] Another single-center, retrospective observational study in elderly patients, including 9 patients with asthma and 11 patients with ACO, showed favorable efficacy of mepolizumab in reducing blood eosinophil levels, OCS use, and exacerbation rates in both groups.[28] The Australian Mepolizumab Registry also showed that mepolizumab significantly reduced exacerbations and improved symptom scores and lung function even in patients with ACO as a comorbidity among patients with severe eosinophilic asthma.[29] Mepolizumab has also been shown to be effective in reducing exacerbations in eosinophilic COPD compared to placebo.[30]

We found no studies on the use of benralizumab in ACO. A study showed that benralizumab had a less clear effect on reducing exacerbations in patients with moderate to severe COPD with elevated blood eosinophils.[31] In a phase 3 trial for eosinophilic COPD, despite a decrease in sputum and blood eosinophils, benralizumab did not significantly reduce exacerbations.[31] Another study showed that the greatest effect of benralizumab was observed in patients with COPD with blood eosinophil levels ≥220 cells/μL, particularly those with severe airflow obstruction of FEV1 <40 % and frequent exacerbations.[32] A phase 2 study is currently underway to evaluate the use of benralizumab in both COPD and asthma (ClinicalTrials.gov Identifier: NCT04098718). The recent clinical trial investigating the use of dupilumab in T2 high (elevated blood eosinophil counts) moderate-to-severe COPD showed better treatment response than placebo.[33] No studies on the use of reslizumab in ACO or COPD were found.

At present, we cannot draw a definitive conclusion regarding the efficacy of asthma biologics in ACO, and more research is needed to determine their role in the management of ACO. Many of the previous studies were clinical trials, and ACO has been excluded from almost all clinical trials of asthma or COPD medications, making real-world research even more important. Our study is 1 of the first real-world studies to investigate which biologics are prescribed for ACO by physicians in a severe asthma registry, as well as treatment effectiveness and prognosis compared to pure asthma. We selected ACO from the severe asthma population using the ATS definition, which includes a

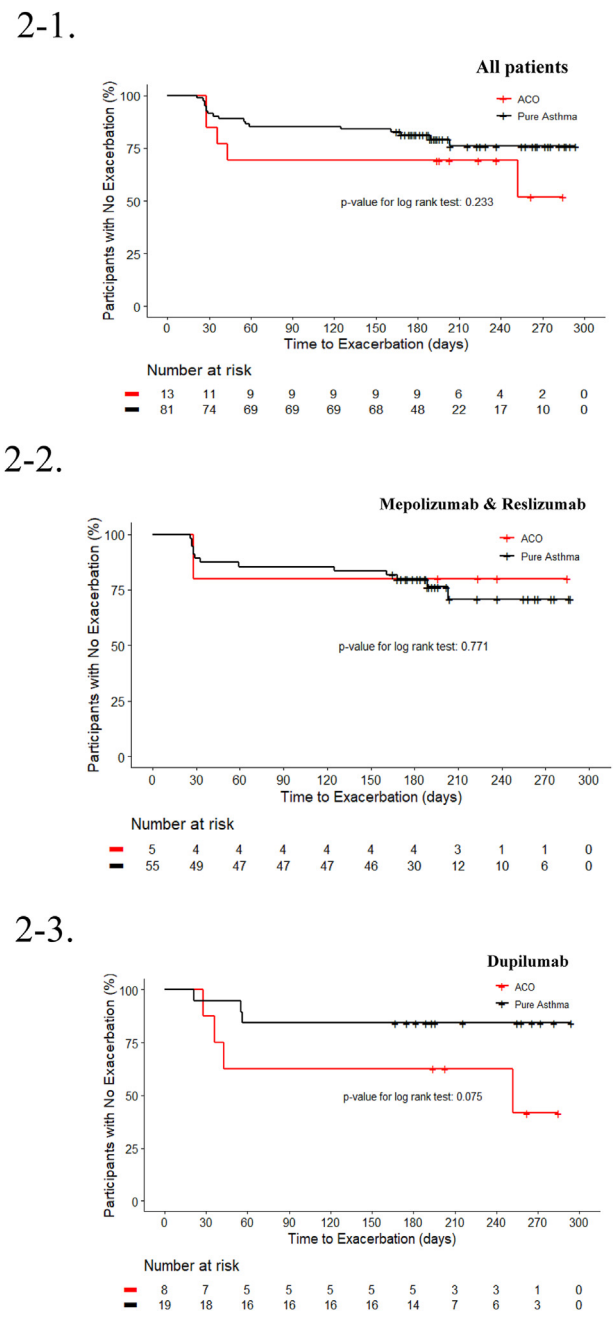

Fig. 2 Kaplan-Meier curves for the time-to-first asthma exacerbation, according to each group. 2-1. ACO vs. Pure asthma 2-2. ACO vs. Pure asthma among mepolizumab and reslizumab users 2-3. ACO vs. Pure asthma among dupilumab users Abbreviations: ACO, asthma-chronic obstructive pulmonary disease overlap.

post-BD FEV/FVC <0.7, age ≥40 years, and a smoking history of at least 10 pack-years.[12]

We identified a single study conducted in a similar setting, utilizing data from the GEMA-DATA register in Spain, which included 297 patients with asthma and 24 patients with ACO.[34] Patients with ACO exhibited lower FEV1 values, but there were no significant differences in other T2 inflammatory biomarkers between the 2 groups.[34] Omalizumab was the most commonly used biologic agent, followed by mepolizumab, benralizumab, and reslizumab.[34] After a 12-month follow-up, the ACO group had a significantly higher proportion of patients experiencing exacerbations than that in the asthma group, and the percentage of controlled patients was significantly lower in the ACO group (16.5 % in ACO vs 39.7 % in asthma).[34] The authors only reported proportions (%) of exacerbated or uncontrolled patients without any adjustments, whereas our study provided fully adjusted odds ratios (ORs) for exacerbation and time-to-first exacerbation.

Our study investigated the treatment responses of biologics in patients with ACO and asthma using real-world cohort data. Our findings showed no significant differences in the improvement of treatment indicators between the ACO and asthma groups following treatment with biologics. Furthermore, even after adjusting for multiple factors, there were no significant differences in the risk of exacerbation. Considering these results, this study provides evidence that treatment with biologics in patients with ACO can result in benefits similar to those observed in patients with asthma.

This study has the following limitations. The most important limitation is the relatively small sample size. If more ACOs using biologics had been included, more convincing and reliable results could have been obtained. However, considering the obstacles of using biologics in real-world settings, it is challenging to recruit a large number of participants for this type of study. Additionally, omalizumab and benralizumab were not used in the ACO group, and this need to be further studied. Another limitation is the relatively short follow-up period of 6 to 9 months. Future studies with longer treatment durations and extended follow-up periods are necessary. Lastly, the results of this study may have limited applicability to populations other than the Korean population.

In conclusion, we consider that the efficacy of biologics in patients with ACO is comparable to that in patients with pure asthma. Therefore, there is no need to refrain from using biologics in ACO

patients; instead, therapeutic options can be considered for treatment based on general criteria for using biologics.

Abbreviations
ACT, asthma control test; ACO, asthma-COPD overlap; BD, bronchodilator; COPD, chronic obstructive pulmonary disease; FeNO, fractional exhaled nitric oxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; ICS, inhaled corticosteroid; IL, interleukin; LABA, long-acting β2-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroid; OR, odds ratio; SCS, systemic corticosteroid; T2, type 2; TFE, time-to-first asthma exacerbation

Funding
This research was supported by the Bio & Medical Technology Development Program of the National Research Foundation (NRF) funded by the Korean government Ministry of Science and ICT (MSIT) (2019M3E5D3073365).

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

Authors' contributions
JS, MH, and TK designed the study; JS, JK, SP, SK, BK, YN, MY, MK, SK, BL, TL, SK, SP, YC, CP, JJ, HP, JK, JC, JM, MK, and TK collected the data; JS and HK analyzed the data; JS, HK, MH, and TK interpreted the data; JS drafted the manuscript; MH, TK, IA, KFC revised the manuscript critically for important intellectual content; all authors critically reviewed and approved the manuscript as submitted and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate
This study was approved by the Institutional Review Board of Ewha Womans University Medical Center (SEUMC 2020-04-014-023) and Asan Medical Center (2019–1676). Informed written consent was obtained from all participants.

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

Submission declaration
The authors confirm that this manuscript is original, has not been published before, is not currently being considered for publication elsewhere, and has not been posted to a preprint server.

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

Acknowledgement
We thank all the members participating in PRISM research group for their support and discussion of the study.

Appendix A. Supplementary data
Supplementary data to this article can be found online at https://doi.org/10.1016/j.waojou.2023.100848.

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