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Differences in asthma-related outcomes by anti-IL-5 biologics, omalizumab, and dupilumab based on blood eosinophil counts

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Abstract

Background: Selecting optimal biologics based on type 2 biomarkers has been of interest in severe asthma treatment. However, few direct biomarker stratification-based comparisons have been made.

Objective: To compare the effectiveness of anti-IL-5 (mepolizumab, benralizumab), omalizumab, and dupilumab in reducing the number of hospitalizations from asthma and exacerbations across all and eosinophil-stratified subgroups.

Methods: A retrospective cohort study using the National Hospital Organization database (2016–2020) was performed. Asthmatic patients using biologics were selected, and the baseline backgrounds of the groups were balanced using inverse probability treatment weighting for propensity scores. Weighted rate ratios (RRs) were obtained using a Poisson regression model.

Results: Among the 320 patients with asthma using biologics, 205 (64.1%), 75 (23.4%), and 40 (12.5%) were categorized into the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, there were 47.1, 30.0, and 62.6 hospitalizations per 100 person-years [omalizumab vs. anti-IL-5: weighted RR, 0.61 (0.34–1.08); dupilumab vs. anti-IL-5: 1.48 (0.81–2.72)], and 117.0, 134.6, and 287.3 exacerbations per 100 person-years [omalizumab vs. anti-IL-5: 1.13 (0.83–1.54); dupilumab vs. anti-IL-5: 2.69 (1.91–3.78)] in these respective groups. In patients with eosinophil of ≥ 300/μL, the dupilumab group had more exacerbations compared with the anti-IL-5 group [weighted RR, 2.85 (1.82–4.46)]. In patients with eosinophil of < 300/μL, the omalizumab group had fewer hospitalizations compared with the anti-IL-5 group [weighted RR, 0.32 (0.13–0.51)].

Conclusions: Anti-IL-5 biologics may be more effective than dupilumab in patients with high blood eosinophil counts, while less effective than omalizumab in patients with low eosinophil counts.

Key words: asthma biologics, eosinophil, IL-5, severe asthma, type 2 inflammation

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Introduction

Asthma affects nearly 400 million people worldwide;[1] of whom, 5–10% are estimated to have severe asthma.[2] Although severe asthma cases comprise a small proportion of all the asthma cases, it is associated with increased mortality and hospitalization, reduced quality of life, and increased healthcare costs.[3-7] New therapies for severe asthma are expected to emerge, and within the last decade, several biologics targeting type 2 inflammation have been developed.[8] Five biologics have been launched as of September 2020, which include anti-IL-5 antibodies (mepolizumab and reslizumab), anti-IL-5 receptor (benralizumab), anti-immunoglobulin E (IgE) (omalizumab), and anti-IL4 receptor α antibodies (dupilumab). In a recent meta-analysis, all the biologics were found to reliably reduce the number of exacerbations, which constitute a significant health risk and are associated with substantial healthcare costs and psychological burden.[9,10]

IL-5 is a principal cytokine responsible for the growth, differentiation, recruitment, activation, and survival of eosinophils. It is also the main target of anti-IL-5 biologics (mepolizumab, reslizumab, and benralizumab). Previous studies have shown that both anti-IL-5 and other biologics have higher effectiveness in patients with higher blood eosinophil count (a type 2 biomarker).[11,12] Hence, it is essential to clarify whether anti-IL-5 biologics are more effective than other biologics in patients stratified according to blood eosinophil count. Although some investigations suggest using blood eosinophil count to determine whether anti-IL-5 or other biologics should be used,[13-15] the differences between these biologics in terms of effectiveness remain uncertain because no head-to-head trials have compared these treatment approaches.

This investigation utilized the National Hospital Organization (NHO) database and compared the effectiveness of these novel therapies in reducing the number of exacerbation events in patients treated with anti-IL-5 biologics, omalizumab, and dupilumab. Additionally, this study aimed to perform subgroup analyses in which patients were categorized into subgroups (blood eosinophil count of ≥ 300/μL or < 300/μL).

Methods

Data source

This retrospective cohort study used the NHO database. The NHO database consists of the medical information analysis (MIA) database, which stores reimbursement reimbursement records, and the national clinical data archives (NCDA), which is an electronic health record database (EHRs).[16-19] The NHO was established in 2004, and as of September 2020, 140 nationwide hospitals were run by the NHO, including acute care and long-term care hospitals. Among these hospitals, 67 joined both the MIA databank and NCDA. The MIA databank holds data from the Diagnosis Procedure Combination (DPC), which includes inpatient demographics and selected clinical information; admission and discharge statuses; and information on diagnosis, surgeries and procedures, medications, and special reimbursements for particular conditions. NCDA provides medical chart information, including daily laboratory data, in a standardized manner. A validation study of the NHO database revealed that the sensitivity and specificity of disease diagnosis using DPC were 78.9% and 93.2%, respectively, and agreement between the NCDA data and chart reviews in terms of laboratory data was >95%.[17]

Patient selection

The study period was the period between the date when a hospital joined the NCDA storage (at least after March 2016) and September 30, 2020. The index date was defined as the date when an asthma biologic was first administered during the study period. The inclusion criteria were as follows: 1) administration record of at least one asthma biologic (omalizumab, mepolizumab, benralizumab, and dupilumab); 2) asthma diagnosis [International Classification of Diseases 10th Revision (ICD-10) code J45/46] before the index date; and 3) at least one prescription record of inhaled corticosteroids (ICS) or ICS/long-acting beta-2-agonist (LABA) within 12 months before the index date. The exclusion criterion was having a diagnosis of eosinophilic granulomatosis with polyangiitis (EGPA; M30.1) before the index date.

Drug prescription and dosages

Identification of the drugs to be used for asthma treatment and calculation of ICS and oral systemic corticosteroid (OCS) dosages were based on the following period (baseline period): from the later of 1 year prior to the index date or the oldest asthma visit with ICS or ICS/LABA prescription within 12 months before the index date to the index date. ICS dosages per day were calculated according to the following formula: (sum of ICS dosages administered in the baseline period) ÷ (number of days × 0.8).[20,21]

As of September 2020, reslizumab had not been approved for use in Japan and was not included in this study. The approved dosages of asthma biologics as of September 2020 in Japan were as follows: omalizumab, every 2–4 weeks according to the total IgE level and body weight at baseline; mepolizumab, at a fixed dosage of 300 mg every 4 weeks; benralizumab, at a dosage of 30 mg every 4 weeks for the first three times and every 8 weeks thereafter; dupilumab, at an initial dosage of 600 mg followed by a dosage of 300 mg every 2 weeks.

Covariates

Patient information such as sex, age, body mass index (BMI), smoking status, Hugh–Jones dyspnea score (a subjective dyspnea score),[22] comorbidities, and drugs prescribed within the baseline period (as defined above), blood test results (eosinophil count and total IgE level), hospitalization, and exacerbation within 12 months before

the index date were included in the analysis. There were a total of 23 variables. Age was categorized into three groups— < 40, 41–60, and > 61 years. BMI was categorized into three groups—underweight (BMI: < 18.50 kg/m^2), normal (18.51–25.00 kg/m^2), and overweight (> 25.01 kg/m^2). Smoking status was divided into two categories—non-smoker and current/ex-smoker. Hugh–Jones score was divided into two categories— 0–3 or 4–5. We identified the following comorbidities based on ICD-10 codes: 1) allergic rhinitis (J30), 2) gastroesophageal reflux disease (GERD; K21), 3) chronic obstructive pulmonary disease (COPD; J43/44), 4) diabetes mellitus (DM; E10-14), 5) chronic paranasal sinusitis (J32), 6) atopic dermatitis (L20), 7) allergic bronchopulmonary mycosis (ABPM; B44.1, B49), and 8) nasal polyp (J33). We identified the following prescribed drugs: LABA, long-acting muscarinic antagonists, leukotriene receptor antagonists, antihistamines, regular OCS, and high-dose ICS. Regular OCS was defined as the case wherein the sum of days for which OCS was prescribed exceeded half of the baseline period. High-dose ICS was defined as the case wherein ICS dosage was equivalent to ≥ 1600-μg/day budesonide. Blood eosinophil count and total IgE level were categorized into the following two groups: –300 or 301–. The maximum values within the baseline period were considered as the results of blood tests.

Exposure and outcomes

The primary exposure of interest was the exposure to anti-IL-5 (mepolizumab and benralizumab), omalizumab, and dupilumab. The anti-IL-5, omalizumab, and dupilumab group were compared in terms of patient characteristics. The treatment period for each patient started from the index date and ended at either 60 days after the last administration of biologics or withdrawal date from the database. If the administration interval exceeded 3 months, the time point immediately before the interval was treated as the last administration date. The primary outcome was hospitalization due to exacerbated asthma, which was confirmed by asthma being the primary diagnosis (ICD-10 code J45/46) combined with a prescription record of an ICS. The secondary outcome was the exacerbation of an asthma-associated event, defined as an event requiring the administration of OCS equivalent to 15-mg/day prednisolone for 3–9 days or of injectable corticosteroids.[20,21] The events occurring within 14 days were treated as the same.

Statistical analyses

We used inverse probability treatment weighting (IPTW) for propensity scores to adjust for potential confounders.[23] The propensity score was estimated using multivariate logistic regression with 23 covariates (listed in **Table 1**).

Table 1. Baseline demographic characteristics of asthma patients using asthma biologics before and after inverse probability weighting (IPTW).

Characteristic	Before IPTW			After IPTW		
	Anti-IL-5 biologics (n = 205)	Omalizumab (n = 75)	Dupilumab (n = 40)	Anti-IL-5 biologics (n = 205)	Omalizumab (n = 75)	Dupilumab (n = 40)
Females	129 (62.9%)	51 (68.0%)	23 (57.5%)	124 (60.6%)	47 (62.0%)	23 (58.4%)
Age, years						
< 40	31 (15.1%)	27 (36.0%)	10 (25.0%)	43 (21.1%)	17 (22.6%)	8 (21.2%)
41–60	48 (23.4%)	12 (16.0%)	14 (35.0%)	42 (20.6%)	13 (17.3%)	9 (22.1%)
> 61	126 (61.5%)	36 (48.0%)	16 (40.0%)	120 (58.3%)	45 (60.1%)	23 (56.8%)
BMI, kg/m^2						
< 18.5	30 (14.6%)	11 (14.8%)	6 (15.3%)	28 (13.7%)	10 (13.0%)	6 (13.8%)
18.51–25.00	106 (51.9%)	46 (61.1%)	15 (37.0%)	99 (48.2%)	38 (50.3%)	18 (45.9%)
> 25.01	69 (33.6%)	18 (24.1%)	19 (47.8%)	78 (38.2%)	28 (36.8%)	16 (40.4%)
Smoking status						
Non-smoker	124 (60.5%)	61 (81.7%)	32 (79.0%)	149 (72.6%)	56 (75.1%)	29 (71.6%)
Current/ex-smoker	81 (39.5%)	14 (18.3%)	8 (21.0%)	56 (27.4%)	19 (24.9%)	11 (28.4%)
Hugh–Jones score						
0–3	129 (62.9%)	52 (68.8%)	31 (77.5%)	143 (69.9%)	51 (68.2%)	29 (73.3%)
4–5	76 (37.1%)	23 (31.2%)	9 (22.5%)	62 (30.1%)	24 (31.8%)	11 (26.7%)

Table 1. (Continued)

Characteristic	Before IPTW			After IPTW		
	Anti-IL-5 biologics (n = 205)	Omalizumab (n = 75)	Dupilumab (n = 40)	Anti-IL-5 biologics (n = 205)	Omalizumab (n = 75)	Dupilumab (n = 40)
Comorbidities						
Allergic rhinitis	45 (22.0%)	18 (24.0%)	5 (12.5%)	45 (22.2%)	17 (23.1%)	8 (21.2%)
GERD	53 (25.9%)	15 (20.0%)	9 (22.5%)	57 (27.9%)	22 (29.5%)	11 (26.9%)
COPD	47 (22.9%)	9 (12.0%)	8 (20.0%)	39 (18.9%)	14 (18.4%)	8 (19.2%)
Diabetes mellitus	42 (20.5%)	16 (21.3%)	9 (22.5%)	38 (18.7%)	14 (19.2%)	7 (16.4%)
Chronic sinusitis	27 (13.2%)	6 (8.0%)	3 (7.5%)	22 (10.6%)	7 (9.7%)	4 (10.7%)
Atopic dermatitis	8 (3.9%)	4 (5.3%)	4 (10.0%)	9 (4.4%)	3 (4.3%)	2 (4.6%)
ABPM	6 (2.9%)	4 (5.3%)	2 (5.0%)	7 (3.5%)	3 (4.4%)	1 (2.7%)
Nasal polyp	2 (1.0%)	0 (0.0%)	0 (0.0%)	1 (0.5%)	0 (0.0%)	0 (0.0%)
Drugs						
LABA	171 (83.4%)	48 (64.0%)	37 (92.5%)	167 (81.6%)	59 (78.6%)	34 (85.0%)
LAMA	76 (37.1%)	27 (36.0%)	18 (45.0%)	89 (43.3%)	33 (43.8%)	17 (43.6%)
LTRA	145 (70.7%)	52 (69.3%)	32 (80.0%)	149 (72.6%)	55 (72.9%)	29 (71.3%)
Antihistamines	79 (38.5%)	24 (32.0%)	25 (62.5%)	93 (45.5%)	33 (43.5%)	20 (49.2%)
Regular OCS	11 (5.4%)	6 (8.0%)	5 (12.5%)	15 (7.2%)	5 (6.2%)	3 (8.2%)
High-dose ICS	21 (10.2%)	7 (9.3%)	6 (15.0%)	19 (9.0%)	6 (8.0%)	4 (9.4%)
Blood test						
Eosinophil count, μL						
< 300	54 (26.5%)	31 (42.0%)	15 (37.7%)	64 (31.3%)	24 (31.5%)	13 (31.6%)
> 301	151 (73.5%)	44 (58.0%)	25 (62.3%)	141 (68.7%)	51 (68.5%)	27 (68.4%)
Total IgE level, IU/mL						
< 300	82 (40.2%)	37 (50.0%)	18 (44.7)	93 (45.6%)	35 (46.5%)	18 (45.7%)
> 301	123 (59.8%)	38 (50.0%)	22 (55.3%)	112 (54.4%)	40 (53.5%)	22 (54.3%)
Event[a]						
Hospitalization	170 (82.9%)	66 (88.0%)	32 (80.0%)	176 (86.0%)	66 (87.6%)	34 (84.6%)
Exacerbation	177 (86.3%)	59 (78.7%)	34 (85.0%)	177 (86.5%)	65 (86.4%)	35 (86.7%)

BMI, body mass index; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; ABPM, allergic bronchopulmonary mycosis; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; ICS, inhaled corticosteroids; smd, standardised mean difference
The number of patients was rounded to the nearest whole number.
[a]Events were defined as those within three months before the index date.

IPTW was then used to balance baseline characteristics between the groups and evaluate average treatment effects. This method produces a pseudo sample of patients weighted by the inverse of the propensity score. The number of patients in each pseudo group was then standardized so that it was equivalent to the original number of patients. Between-group differences in baseline characteristics observed before and after IPTW were compared using standardized mean difference (differences ≤ 10% were treated as well balanced).[24]

Weighted rate ratios (RRs) and 95% confidence intervals (CIs) of the primary and secondary outcomes were calculated using a Poisson regression model (with the logarithm of the length of observational periods as the offset). The model was adjusted for within-hospital clustering by employing a robust variance estimator, resulting in unbiased standard error estimators for regression coefficients in cluster-correlated data with large sample size and sufficient events.[25] Missing covariate data were imputed using multiple imputations

via a chained equation on the assumption that data were missing at random (10 imputed datasets were prepared; See **Supplementary Table S1** for covariates with missing data before and after performing multiple imputations).[26] Finally, the results for each imputed dataset were aggregated using Rubin's rule.[27]

In a secondary analysis, prespecified subgroup analyses were conducted according to blood eosinophil count (either ≥ 300/μL or < 300/μL). Analyses were performed in a manner similar to that described above. However, due to the decrease in sample size, we estimated the propensity score using the covariates without comorbidities and drugs.

We did four sensitivity analyses to assess the robustness of the findings for the outcomes. The duration between the observation start date and the index date was sufficiently long (median 1000 days [interquartile range (IQR), 153–2251]), so we did not require the study population to have a specific duration range. To account for the possibility that the results in the primary analysis might be biased due to the inclusion of populations without a specific duration range, we conducted a sensitivity analysis that excluded those populations lacking a period of at least 365 days in duration. Secondly, we changed the blood eosinophil count cutoff value from 300/μL to 450/μL due to the inherent variability in eosinophil counts. Thirdly, we limited the study population to those not using regular oral corticosteroids because eosinophil count can be influenced by corticosteroids use. Fourthly, we limited the study population to those with an observational period of at least 120 or 180 days and fixed the observational period at 120 or 180 days because the observational periods varied across biologic groups and could affect the outcomes.

Because of the potential type 1 error resulting from multiple comparisons, findings from secondary outcomes and secondary analyses should be interpreted as exploratory. A *P*-value < 0.05 was considered statistically significant. All statistical analyses were performed using R software (v3.6.3; R Core Team 2020).[28] The article was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology Statement (See **Supplementary Table S2**).

Ethics statement

This study was conducted ethically in accordance with World Medical Association Declaration of Helsinki. It was approved by the institutional review board of NHO Tokyo Hospital (approval no.: 200067). Owing to the retrospective nature of the study, the requirement of written informed consent was waived.

Results

Patients

Table 1 shows patient characteristics for each study group. Overall, 352 patients who met our inclusion criteria were included in the analysis. Of these, 32 patients who had a diagnosis of EGPA before the index date were excluded. Finally, 320 patients [203 (63.4%) females] with a median age of 64 years [interquartile range (IQR), 44–74] were enrolled (shown in **Figure 1**). In total, 205 patients (64.1%; 121 using mepolizumab and 84 using benralizumab), 75 patients (23.4%), and 40 patients (12.5%) were categorized into the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, the two groups were found to be well balanced for the 23 variables (shown in **Table 1** and **Figure 2**).

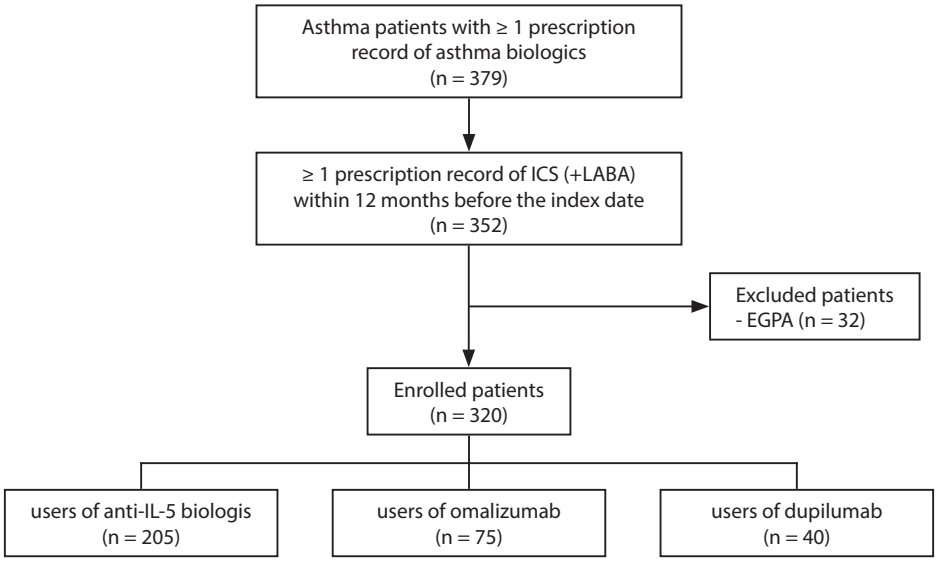

Figure 1. Patient flow chart.

ICS, inhaled corticosteroids; LABA, long-acting beta-agonist; EGPA, eosinophilic granulomatosis with polyangiitis

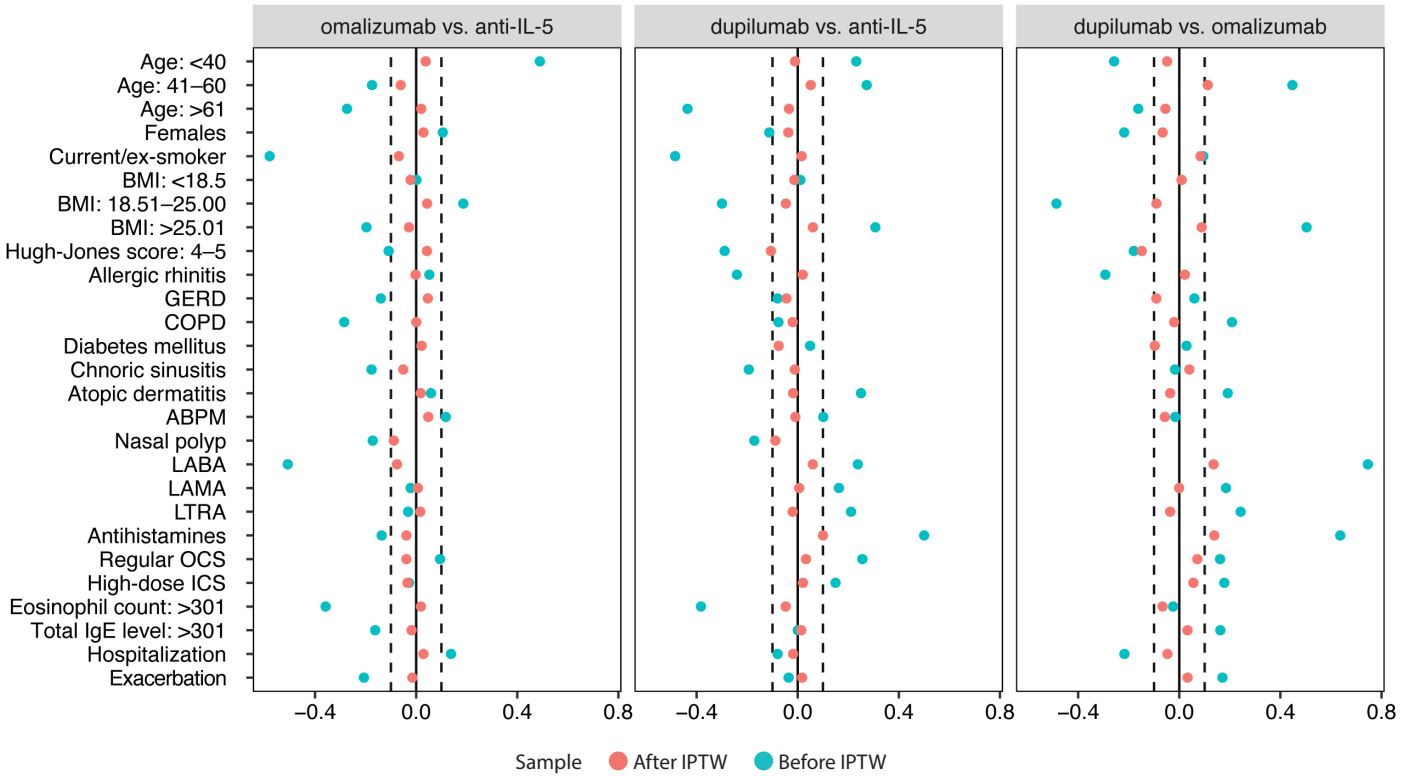

Figure 2. Standardized mean differences in baseline characteristics of the patients with asthma using asthma biologics, before and after ITPW.

IPTW, inverse probability treatment weighting; BMI, body mass index; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; ABPM, allergic bronchopulmonary mycosis; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; ICS, inhaled corticosteroids
The dotted line represents 0.1.

The median observational periods were 260 [IQR, 89–603], 412 [117–815], and 151 [29–321] days for the anti-IL-5, omalizumab, and dupilumab groups, respectively.

Entire cohort

There were 40.8, 30.9 and 57.4 hospitalizations per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, there were 47.1, 30.0, and 62.6 hospitalizations per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. There were no between-group differences in hospitalization rates (shown in **Table 2**). Originally, the dupilumab group was associated with a higher number of exacerbation events compared with the anti-IL-5 group [dupilumab group vs. anti-IL-5 group: 217.7 vs. 106.3 exacerbation events per 100 person-years; RR, 1.97 (1.37–2.83)]. Even after weighting, the dupilumab group was associated with a higher number of exacerbation events [weighted RR, 2.69 (1.91–3.78)]. No significant differences in exacerbation rates were observed between the anti-IL-5 and omalizumab groups.

Cohort consisting of patients with blood eosinophil count of ≥ 300/μL

A total of 151, 44, and 25 patients with blood eosinophil count of ≥ 300/μL were categorized into the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, the three groups were found to be well balanced (shown in **Figure S1**).

There were 33.7, 30.8, and 46.7 hospitalizations per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, there were 34.5, 26.8, and 55.5 hospitalizations per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. The hospitalization rates of the groups were not different between groups (shown in **Table 3**). Originally, the dupilumab group was associated with a higher number of exacerbation events compared with the anti-IL-5 group [dupilumab group vs. anti-IL-5 group: 226.5 vs. 90.3 exacerbation events per 100 person-years; RR, 2.36 (1.47–3.79)]. Even after weighting, the dupilumab group was associated with a higher number of exacerbation events [weighted RR, 2.85 (1.82–4.46)]. No significant differences in exacerbation rates were observed between the anti-IL-5 and omalizumab groups.

Table 2. Summary of unadjusted/adjusted event rate parameters in the entire cohort.

Parameter	Unweighted			Weighted[a]		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	205	75	40	205	75	40
Number of patient-years	235.1	113.3	41.8	220.6	106.1	66.0
Number of hospitalizations	96	35	24	104	32	41
Rate per 100 person-years	40.8	30.9	57.4	47.1	30.0	62.6
Rate ratio (vs. reference; 95%CI)	Reference	0.77 (0.44–1.33)	1.68 (0.89–3.18)	Reference	0.61 (0.34–1.08)	1.48 (0.81–2.72)
Number of exacerbations	250	134	91	258	143	190
Rate per 100 person-years	106.3	118.3	217.7	117.0	134.6	287.3
Rate ratio (vs. reference; 95%CI)	Reference	1.07 (0.78–1.48)	**1.97 (1.37–2.83)**	Reference	1.13 (0.83–1.54)	**2.69 (1.91–3.78)**

[a]Inverse probability of treatment weighting (IPTW) on the propensity score for sex, age, body mass index, smoking status, hugh-jones score, comorbidities, used drugs, blood tests (eosinophil and total IgE) and hospitalisation/exacerbations within three months before the index date.

Table 3. Summary of unadjusted/adjusted event rate parameters in patients whose eosinophil ≥ 300/microliter.

Parameter	Unweighted			Weighted[a]		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	151	44	25	151	44	25
Number of patient-years	181.5	70.2	23.3	173.6	55.4	22.4
Number of hospitalizations	61	22	11	60	15	12
Rate per 100 person-years	33.7	30.8	46.7	34.5	26.8	55.5
Rate ratio (vs. reference; 95%CI)	Reference	0.92 (0.45–1.87)	1.28 (0.45–3.63)	Reference	0.78 (0.36–1.69)	1.50 (0.59–3.83)
Number of exacerbations	164	69	53	164	58	64
Rate per 100 person-years	90.3	98.8	226.5	94.2	105.0	284.7
Rate ratio (vs. reference; 95%CI)	Reference	1.10 (0.74–1.64)	**2.36 (1.47–3.79)**	Reference	1.11 (0.73–1.70)	**2.85 (1.82–4.46)**

[a]Inverse probability of treatment weighting (IPTW) on the propensity score for sex, age, body mass index, smoking status, Hugh-Jones' score, blood tests (Total IgE) and hospitalisation/exacerbations within three months before the index date.

Cohort consisting of patients with blood eosinophil count of < 300/μL

A total of 54, 31, and 15 patients with blood eosinophil count of < 300/μL were categorized into the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, the three groups were found to be well balanced (shown in **Figure S2**).

There were 64.6, 31.1, and 66.5 hospitalizations per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, there were 60.8, 19.9, and 69.6 hospitalizations per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. The omalizumab group was associated with fewer hospitalizations compared with the anti-IL-5 group [weighted RR, 0.32 (0.13–0.51)] (shown in **Table 4**). There were 158.7, 149.2, and 205.5 exacerbation events per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. After weighting, there were 144.9, 143.2, and 224.6 exacerbation events per 100 person-years in the anti-IL-5, omalizumab, and dupilumab groups, respectively. No significant differences in exacerbation rates were observed between groups.

As supplementary information, there were a total of 24, 13 and 6 patients with blood eosinophil count of < 150/μL were categorized into the anti-IL-5, omalizumab, and dupilumab groups, respectively.

Table 4. Summary of unadjusted/adjusted event rate parameters in patients whose eosinophil < 300/microliter.

Parameter	Unweighted			Weighted[a]		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	54	31	15	54	31	15
Number of patient-years	53.7	43.1	18.5	55.7	47.2	18.4
Number of hospitalizations	35	13	12	34	9	13
Rate per 100 person-years	64.6	31.1	66.5	60.8	19.9	69.6
Rate ratio (vs. reference; 95%CI)	Reference	0.48 (0.21–1.13)	1.00 (0.39–2.53)	Reference	**0.32 (0.13–0.51)**	1.14 (0.47–2.77)
Number of exacerbations	85	64	38	81	68	41
Rate per 100 person-years	158.7	149.2	205.5	144.9	143.2	224.6
Rate ratio (vs. reference; 95%CI)	Reference	0.94 (0.58–1.54)	1.18 (0.63–2.21)	Reference	0.99 (0.63–1.56)	1.49 (0.83–2.65)

[a]Inverse probability of treatment weighting (IPTW) on the propensity score for sex, age, body mass index, smoking status, Hugh-Jones' score, blood tests (Total IgE) and hospitalisation/ exacerbations within three months before the index date

Sensitivity analysis

After excluding those populations lacking a period of at least 365 days prior to the index date, a total of 167, 59, and 32 patients were categorized into the anti-IL-5, omalizumab, and dupilumab groups, respectively. Similar to the primary analysis, no differences between groups were observed in terms of hospitalization, and the dupilumab group was associated with a higher number of exacerbation events compared with the anti-IL-5 group, both before and after weighting (shown in **Table S3**).

In the analysis changing the blood eosinophil count cutoff value from 300/μL to 450/μL, the results were consistent: in the cohort consisting of patients with blood eosinophil count of ≥ 450/μL, the dupilumab group was associated with a higher number of exacerbation events, both before and after weighting (shown in **Table S4**); in the cohort consisting of patients with blood eosinophil count of < 450/μL, the omalizumab group was associated with fewer hospitalizations compared with the anti-IL-5 group after weighting (shown in **Table S5**).

In the analysis limiting the study population to those not using regular OCS, the results were largely consistent with the primary analysis, except for the point that the unweighted/weighted event rate of hospitalizations between the omalizumab and anti-IL-5 group reached significance (shown in **Table S6**).

After limiting the study population to those with an observational period of at least 120 or 180 days and fixing the observational period at 120 or 180 days, the resutls were almost similar to those in the primary analysis (shown in **Table S7 and S8**).

Discussion

The principal novel finding of this study is that anti-IL-5 (mepolizumab and benralizumab) biologics resulted in a more significant reduction in exacerbations compared with dupilumab. The findings persisted even in patients with blood eosinophil count of ≥ 300/μL, but was not observed in patients with blood eosinophil count of < 300/μL. Additionally, anti-IL-5 biologics were associated with more hospitalizations compared with omalizumab in patients with blood eosinophil count of < 300/μL. However, this association was not observed in the entire patients or in patients with blood eosinophil count of ≥ 300/μL.

According to a recent systematic review assessing 14 randomized controlled trials (RCTs) (5 for omalizumab, 3 for mepolizumab, 3 for benralizumab, and 3 for dupilumab) including patients aged 12–75 years, all biologics used currently can reliably reduce exacerbation rates [pooled incidence ratios: 0.56 (95%CI, 0.40–0.77) for omalizumab, 0.49 (0.38–0.66) for mepolizumab, 0.53 (0.39–0.72) for benralizumab, and 0.43 (0.32–0.59) for dupilumab].[10] Although direct comparisons could not be performed because such RCTs usually vary in terms of their definitions for enrolled patients, outcomes, and study durations, the reduction rates seemed similar across treatments.[29] This study used a single database that contained information regarding all four biologics and, therefore, may be less biased than studies that use multiple data sources. Although a network meta-analysis using indirect head-to-head comparisons reported no superiority of any included biologics in terms of exacerbation rate,[29] our results for the entire cohort, which were adjusted for potential confounding variables (including blood eosinophil count and total IgE level) suggested that anti-IL-5 biologics were more effective in reducing exacerbation rates compared with dupilumab.

Some reports have suggested that blood eosinophil count should be used to determine the optimal asthma biologic.[13-15,30] These suggestions were based on the theoretical assumption that patients with a higher number of eosinophils, which are the primary target of anti-IL-5 biologics, are expected to have a greater therapeutic effect, as well as on the results of previous RCTs showing that the suppressive effects of anti-IL-5 on exacerbations is higher in patients with more eosinophils compared with those with fewer. Our results indicate that in patients with high blood eosinophil counts, anti-IL-5 may be more effective than dupilumab, whereas its effectiveness may be weaker in patients with omalizumab, partly supporting the above suggestions. Anti-IL-5 biologics directly target eosinophils, which might make their effectiveness more influenced by eosinophil counts compared to omalizumab and dupilumab. Future studies are needed to verify the reproducibility of our results and to conduct comparative analyses of asthma biologics' effectiveness based not only on eosinophils but also on multiple type 2 biomarkers.

This study has some limitations. First, each biologic included in this study was approved for use in Japan at different times (omalizumab, 2009; mepolizumab, 2016; benralizumab, 2018; and dupilumab, 2019), and the observational periods were different for the groups. We employed an offset term of the logarithm of the length of observational periods to address this problem. Second, the number of outcomes and the drug prescription and dosages (e.g., ICS) may be underestimated because we could only identify outcomes and drug prescription and dosages used in NHO hospitals. However, the rates of outcomes were not different compared to those of a previous real-world study investigating the effectiveness of biologics.[21,31] Third, although we set the cutoff value for blood eosinophil count at 300/μL based on previous reports that adopted this value for selecting optimal biologics,[13-15,30] there is no definitive value. While we changed the value to 450 and confirmed the robustness of the results, further analyses using different cutoff values will be necessary. Fourth, our results could be affected by asthma biologics prescribed before the inclusion in our database or those prescribed at hospitals other than NHO hospitals. Regarding the former issue of previous prescriptions, we confirmed that the period from the observation start date to the index date (window period) was sufficiently long (median 1000 days [IQR, 153–2251]). Additionally, we found that the results of the sensitivity analysis were consistent with those of the primary analysis. As for the latter issue of prescriptions at non-NHO hospitals, future research using a database that covers all medical institutions should be conducted. Fifth, we used Hugh–Jones score as the subjective measurement of dyspnea; however, data on pulmonary function tests were not available in the database. Therefore, our results might be unfavorably affected by those patients whose Hugh–Jones score did not correlate with their pulmonary function tests. Sixth, we could not extract data on fractional exhaled nitric oxide from the database because it was not stored in an extractable format. Finally, despite using the propensity score-based methods to minimize bias, confounding by indication due to unmeasured covariates may remain. Additionally, because this is an observational study, causal associations could not be established.

In conclusion, in patients treated with asthma biologics, anti-IL-5 biologics may be more effective than dupilumab in patients with high blood eosinophil counts, while less effective than omalizumab in patients with low blood eosinophil counts.

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Conflict of interest

Norihiko Inoue, Shinobu Imai, and Hirotoshi Matsui declare no conflict of interest. Yuya Kimura received Grant of The Clinical Research Promotion Foundation 2022. Maho Suzukawa received research funding from Shionogi, MSD, Sanofi, Kyorin, AstraZeneca, and GlaxoSmithKline. Manabu Akazawa received fees for consulting or lectures from Takeda, Shionogi, and Astellas Pharma.

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Author contributions

- Conceptualization, Y.K.
- Methodology, Y.K., N.I., S.I. and M.A.
- Software, Y.K., N.I.
- Validation, Y.K., N.I.
- Formal analysis, Y.K., N.I.
- Investigation, Y.K., N.I.
- Writing original draft preparation, Y.K.
- Writing review and editing, Y.K., M.S., N.I., S.I., M.H., M.A. and H.M.
- Supervision, H.M.
- All authors have read and agreed to the published version of the manuscript.

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Supporting Information Legends

Table S1. Before and After multiple imputation.

Characteristic	Before MI			After MI		
	Anti-IL-5 biologics (n = 205)	Omalizumab (n = 75)	Dupilumab (n = 40)	Anti-IL-5 biologics (n = 205)	Omalizumab (n = 75)	Dupilumab (n = 40)
BMI, kg/m^2						
< 18.5	28 (13.7%)	10 (13.3%)	6 (15.0%)	30 (14.6%)	11 (14.8%)	6 (15.3%)
18.51–25.00	103 (50.2%)	45 (60.0%)	14 (35.0%)	106 (51.9%)	46 (61.1%)	15 (37.0%)
> 25.01	67 (32.7%)	18 (24.0%)	19 (47.5%)	69 (33.6%)	18 (24.1%)	19 (47.8%)
missing	7 (3.4%)	2 (2.7%)	1 (2.5%)	-	-	-
Smoking status						
Non-smoker	109 (53.2%)	56 (74.7%)	26 (65.0%)	124 (60.5%)	61 (81.7%)	32 (79.0%)
Current/ex-smoker	68 (33.2%)	11 (14.7%)	6 (15.0%)	81 (39.5%)	14 (18.3%)	8 (21.0%)
missing	28 (13.7%)	8 (10.7%)	8 (20.0%)	-	-	-
Hugh–Jones score						
0–3	122 (59.5%)	49 (65.3%)	31 (77.5%)	129 (62.9%)	52 (68.8%)	31 (77.5%)
4–5	71 (34.6%)	23 (30.7%)	9 (22.5%)	76 (37.1%)	23 (31.2%)	9 (22.5%)
missing	12 (5.9%)	3 (4.0%)	0 (0.0%)	-	-	-
Blood test						
Eosinophil count, μL						
< 300	53 (25.9%)	34 (45.3%)	17 (42.5%)	54 (26.5%)	31 (42.0%)	15 (37.7%)
> 301	108 (52.7%)	30 (40.0%)	15 (37.5%)	151 (73.5%)	44 (58.0%)	25 (62.3%)
missing	44 (21.5%)	11 (14.7%)	8 (20.0%)	-	-	-
Total IgE level, IU/mL						
< 300	49 (23.9%)	26 (34.7%)	11 (27.5%)	82 (40.2%)	37 (50.0%)	18 (44.7)
> 301	83 (40.5%)	28 (37.3%)	12 (30.0%)	123 (59.8%)	38 (50.0%)	22 (55.3%)
missing	73 (35.6%)	21 (28.0%)	17 (42.5%)	-	-	-

MI, multiple imputation; BMI, body mass index
The number of patients was rounded to the nearest whole number.

Table S2. TableSTROBE Statement.

	Item No	Recommendation	Page No
Title and abstract	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	3 3, 4
Introduction			
Background/ rationale	2	Explain the scientific background and rationale for the investigation being reported	4, 5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	11, 12
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6, 7
Participants	6	(a) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up (b) For matched studies, give matching criteria and number of exposed and unexposed	6, 7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-10
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-10
Bias	9	Describe any efforts to address potential sources of bias	10-12
Study size	10	Explain how the study size was arrived at	6-7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-10
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) If applicable, explain how loss to follow-up was addressed (e) Describe any sensitivity analyses	10-12 11, 12 11
Results			
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed (b) Give reasons for non-participation at each stage (c) Consider use of a flow diagram	13, Figure 1. 13, Figure 1. Figure 1.
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders (b) Indicate number of participants with missing data for each variable of interest (c) Summarise follow-up time (eg, average and total amount)	Table 1 Table S1
Outcome data	15*	Report numbers of outcome events or summary measures over time	13-17, Table 2-4

MI, multiple imputation; BMI, body mass index
The number of patients was rounded to the nearest whole number.

Table S3. Summary of unweighted/weighted event rate parameters in patients with at least one year of baseline period.

Parameter	Unweighted			Weighted*		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	167	59	32	167	59	32
Number of patient-years	195.4	87.3	39.4	182.7	72.5	45.8
Number of hospitalizations	77	29	23	89	32	32
Rate per 100 person-years	39.4	33.2	58.4	48.9	43.8	70.5
Rate ratio (vs. reference; 95%CI)	Reference	0.83 (0.44–1.56)	1.67 (0.85–3.27)	Reference	0.57 (0.30–1.10)	1.67 (0.85–3.28)
Number of exacerbations	223	108	90	224	95	142
Rate per 100 person-years	114.2	123.7	228.5	122.5	131.4	310.8
Rate ratio (vs. reference; 95%CI)	Reference	1.00 (0.70–1.43)	**1.85 (1.27–2.70)**	Reference	0.94 (0.64–1.38)	**2.29 (1.55–3.39)**

CI, confidence interval
*Inverse probability treatment weighting for the propensity scores of sex, age, body mass index, smoking status, Hugh–Jones score, comorbidities, drugs used, blood test results (eosinophil count and total IgE level), and hospitalizations/exacerbations occurring within 12 months prior to the index date.

Table S4. Summary of unweighted/weighted event rate parameters in patients with an eosinophil count of ≥ 450 μL.

Parameter	Unweighted			Weighted*		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	140	37	19	140	37	19
Number of patient-years	168.9	61.2	18.7	217.9	104.7	64.9
Number of hospitalizations	58	21	7	80	39	26
Rate per 100 person-years	34.1	34.1	39.3	36.8	37.1	39.4
Rate ratio (vs. reference; 95%CI)	Reference	1.00 (0.48–2.11)	0.96 (0.22–4.14)	Reference	1.00 (0.45–2.19)	0.68 (0.09–4.92)
Number of exacerbations	156	60	45	185	112	174
Rate per 100 person-years	92.1	98.7	238.9	84.7	107.4	268.3
Rate ratio (vs. reference; 95%CI)	Reference	1.07 (0.70–1.64)	**2.38 (1.41–4.03)**	Reference	1.27 (0.77–2.08)	**2.45 (1.29–4.65)**

CI, confidence interval
*Inverse probability treatment weighting for the propensity scores of sex, age, body mass index, smoking status, Hugh–Jones score, blood test results (total IgE level), and hospitalizations/exacerbations occurring within 12 months prior to the index date.

Table S5. Summary of unweighted/weighted event rate parameters in patients with an eosinophil count of < 450/μL.

Parameter	Unweighted			Weighted*		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	65	38	21	65	38	21
Number of patient-years	66.2	52.1	23.1	64.9	54.4	19.1
Number of hospitalizations	38	14	16	39	12	15
Rate per 100 person-years	57.9	27.0	70.0	60.5	22.7	77.5
Rate ratio (vs. reference; 95%CI)	Reference	0.47 (0.21–1.06)	1.20 (0.54–2.67)	Reference	**0.39 (0.16–0.90)**	1.30 (0.57–2.97)
Number of exacerbations	94	73	49	92	85	37
Rate per 100 person-years	141.5	140.5	212.9	141.5	156.4	191.6
Rate ratio (vs. reference; 95%CI)	Reference	1.00 (0.63–1.58)	1.43 (0.83–2.47)	Reference	1.12 (0.74–1.72)	1.33 (0.74–2.37)

CI, confidence interval
*Inverse probability treatment weighting for the propensity scores of sex, age, body mass index, smoking status, Hugh–Jones score, blood test results (total IgE level), and hospitalizations/exacerbations occurring within 12 months prior to the index date.

Table S6. Summary of unweighted/weighted event rate parameters in patients not using regular oral corticosteroids.

Parameter	Unweighted			Weighted*		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	194	69	35	194	69	35
Number of patient-years	230.2	95.9	39.8	209.9	83.0	53.4
Number of hospitalizations	91	24	22	103	18	29
Rate per 100 person-years	39.5	25.0	55.3	49.3	21.9	55.1
Rate ratio (vs. reference; 95%CI)	Reference	**0.52 (0.27–0.97)**	1.58 (0.83–3.04)	Reference	**0.34 (0.16–0.71)**	1.22 (0.63–2.39)
Number of exacerbations	242	92	86	242	88	161
Rate per 100 person-years	105.1	95.9	216.1	115.3	106.1	301.8
Rate ratio (vs. reference; 95%CI)	Reference	0.84 (0.59–1.19)	**1.85 (1.28–2.66)**	Reference	0.85 (0.59–1.23)	**2.45 (1.70–3.53)**

CI, confidence interval
*Inverse probability treatment weighting for the propensity scores of sex, age, body mass index, smoking status, Hugh–Jones score, blood test results (total IgE level), and hospitalizations/exacerbations occurring within 12 months prior to the index date.

Table S7. Summary of unweighted/weighted event rate parameters in patients with at least 120 days of observational period.

Parameter	Unweighted			Weighted*		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	141	56	21	141	56	21
Number of patient-years	46.4	18.4	6.9	46.4	18.4	6.9
Number of hospitalizations	29	11	8	30	6	10
Rate per 100 person-years	62.6	59.7	115.9	65.2	30.1	149.3
Rate ratio (vs. reference; 95%CI)	Reference	0.94 (0.41–2.15)	2.25 (0.86–5.90)	Reference	0.45 (0.17–1.19)	**2.55 (1.06–6.14)**
Number of exacerbations	61	31	14	60	30	15
Rate per 100 person-years	131.6	168.4	202.8	128.8	163.4	224.0
Rate ratio (vs. reference; 95%CI)	Reference	1.15 (0.65–2.02)	1.53 (0.73-3.21)	Reference	1.10 (0.62–1.94)	1.69 (0.83–3.46)

CI, confidence interval

*Inverse probability treatment weighting for the propensity scores of sex, age, body mass index, smoking status, Hugh–Jones score, blood test results (total IgE level), and hospitalizations/exacerbations occurring within 12 months prior to the index date.

Table S8. Summary of unweighted/weighted event rate parameters in patients with at least 180 days of observational period.

Parameter	Unweighted			Weighted*		
	Anti-IL-5 biologics	Omalizumab	Dupilumab	Anti-IL-5 biologics	Omalizumab	Dupilumab
Number of patients	123	48	18	123	48	18
Number of patient-years	60.7	23.7	8.9	60.7	23.7	8.9
Number of hospitalizations	34	11	8	34	6	9
Rate per 100 person-years	56.1	46.5	90.1	56.6	24.7	95.7
Rate ratio (vs. reference; 95%CI)	Reference	0.61 (0.24–1.57)	2.32 (0.76–7.05)	Reference	0.37 (0.13–1.05)	1.79 (0.59–5.42)
Number of exacerbations	76	36	21	73	27	18
Rate per 100 person-years	125.3	152.1	236.6	119.8	113.1	203.6
Rate ratio (vs. reference; 95%CI)	Reference	1.03 (0.59–1.78)	1.84 (0.96–3.54)	Reference	0.82 (0.45–1.50)	1.71 (0.85–3.44)

CI, confidence interval

*Inverse probability treatment weighting for the propensity scores of sex, age, body mass index, smoking status, Hugh–Jones score, blood test results (total IgE level), and hospitalizations/exacerbations occurring within 12 months prior to the index date.

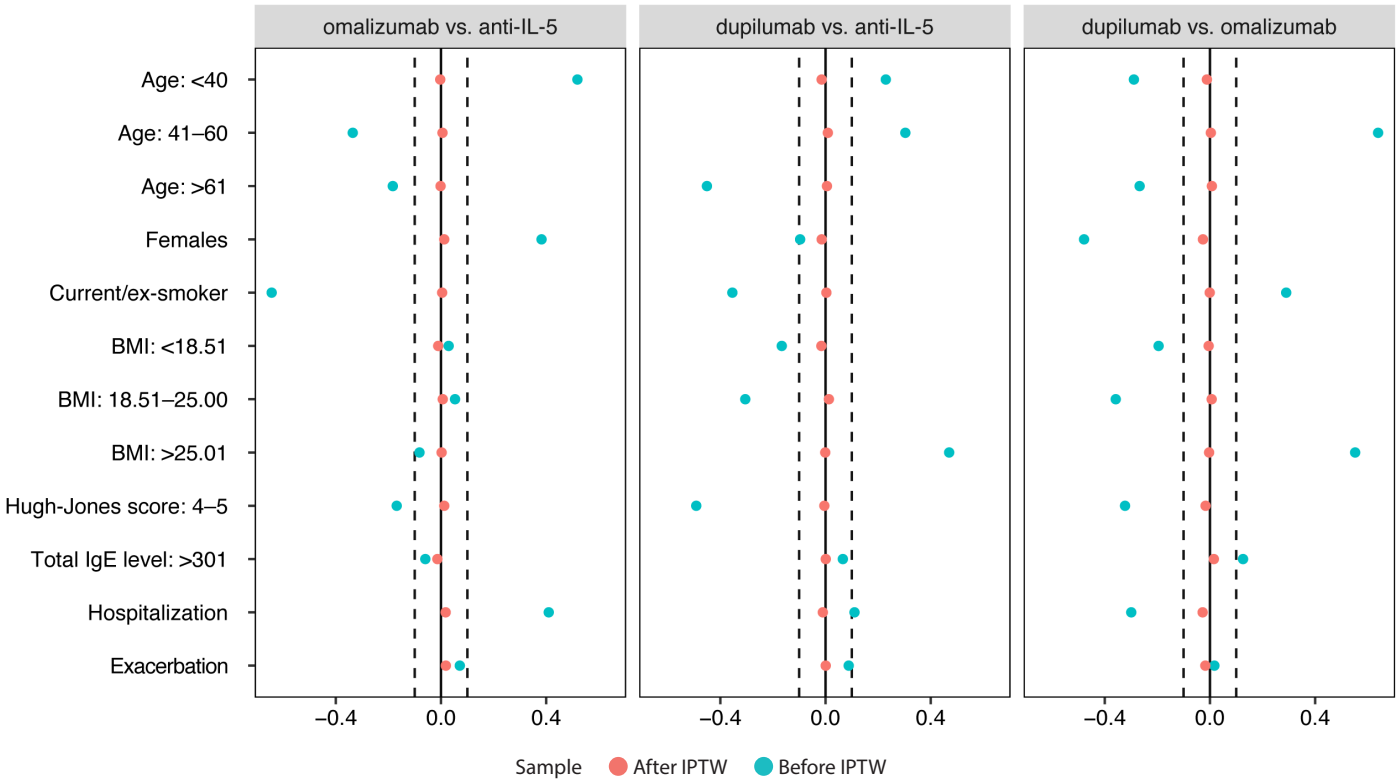

Figure S1. Standardized mean differences in baseline characteristics of the patients with asthma and an eosinophil count of ≥ 300/μL using asthma biologics, before and after ITPW.

IPTW, inverse probability treatment weighting; BMI, body mass index
The dotted line represents 0.1.

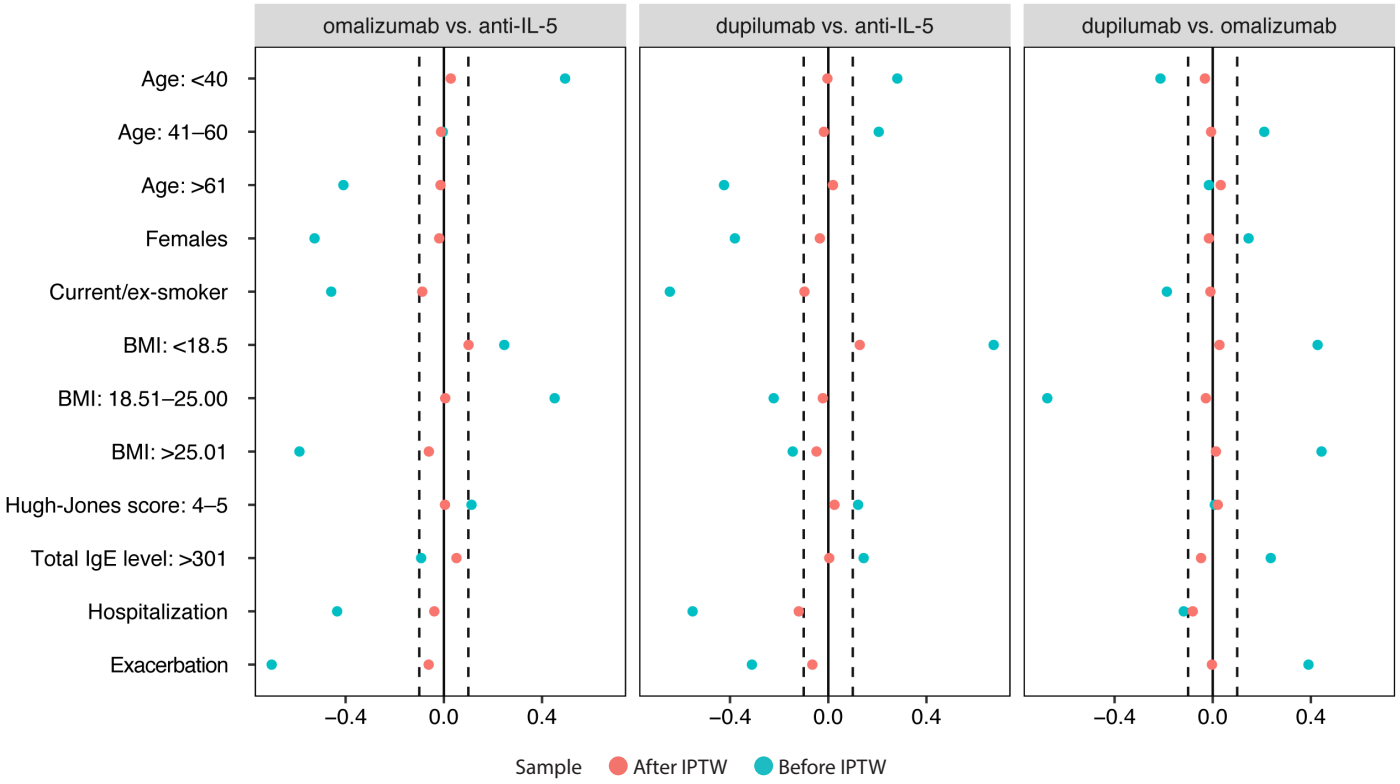

Figure S2. Standardized mean differences in baseline characteristics of the patients with asthma and an eosinophil count of < 300/μL using asthma biologics, before and after ITPW

IPTW, inverse probability treatment weighting; BMI, body mass index
The dotted line represents 0.1.

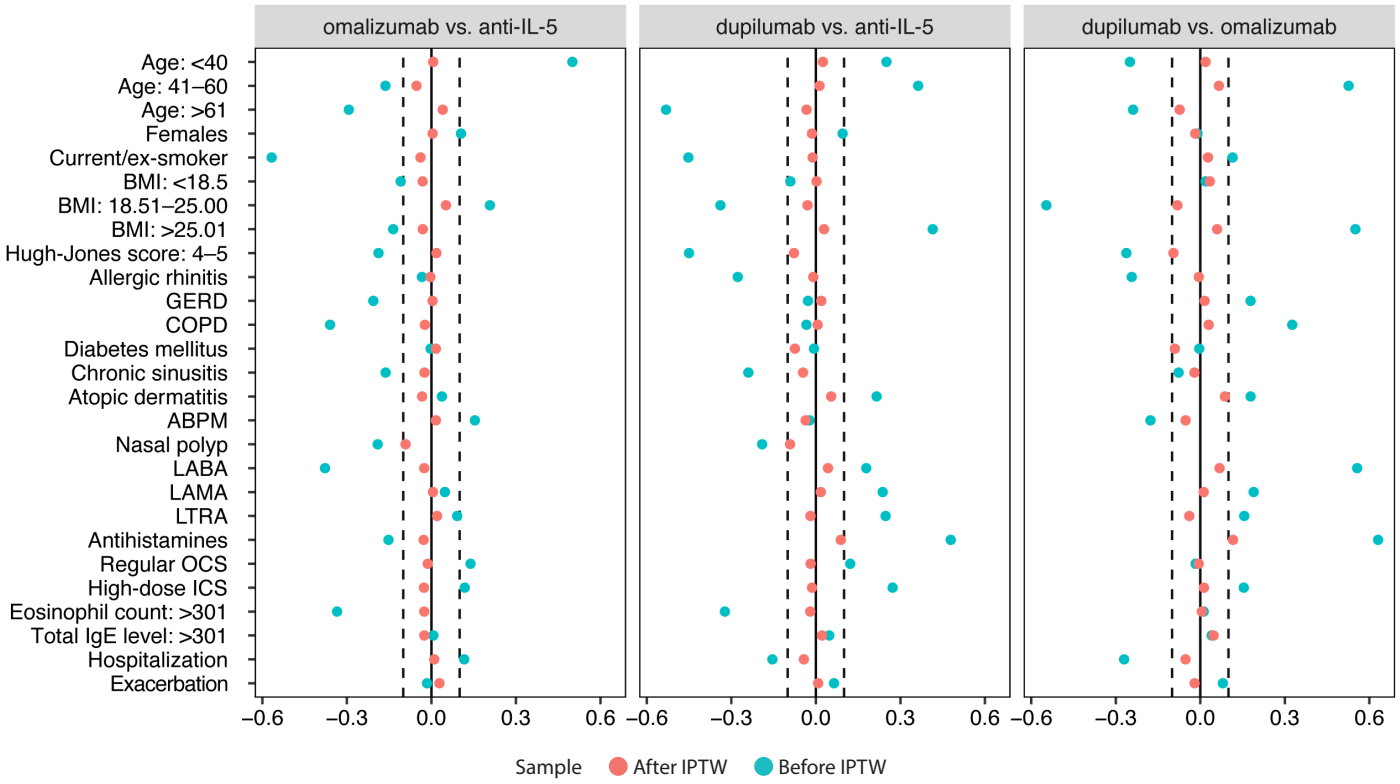

Figure S3. Standardized mean differences in baseline characteristics of the patients with asthma using asthma biologics in the sensitivity analysis, before and after ITPW.

IPTW, inverse probability treatment weighting; BMI, body mass index; GERD, gastroesophageal reflux disease; COPD, chronic obstructive pulmonary disease; ABPM, allergic bronchopulmonary mycosis; LABA, long-acting beta-agonist; LAMA, long-acting muscarinic antagonist; LTRA, leukotriene receptor antagonist; OCS, oral corticosteroids; ICS, inhaled corticosteroids
The dotted line represents 0.1.

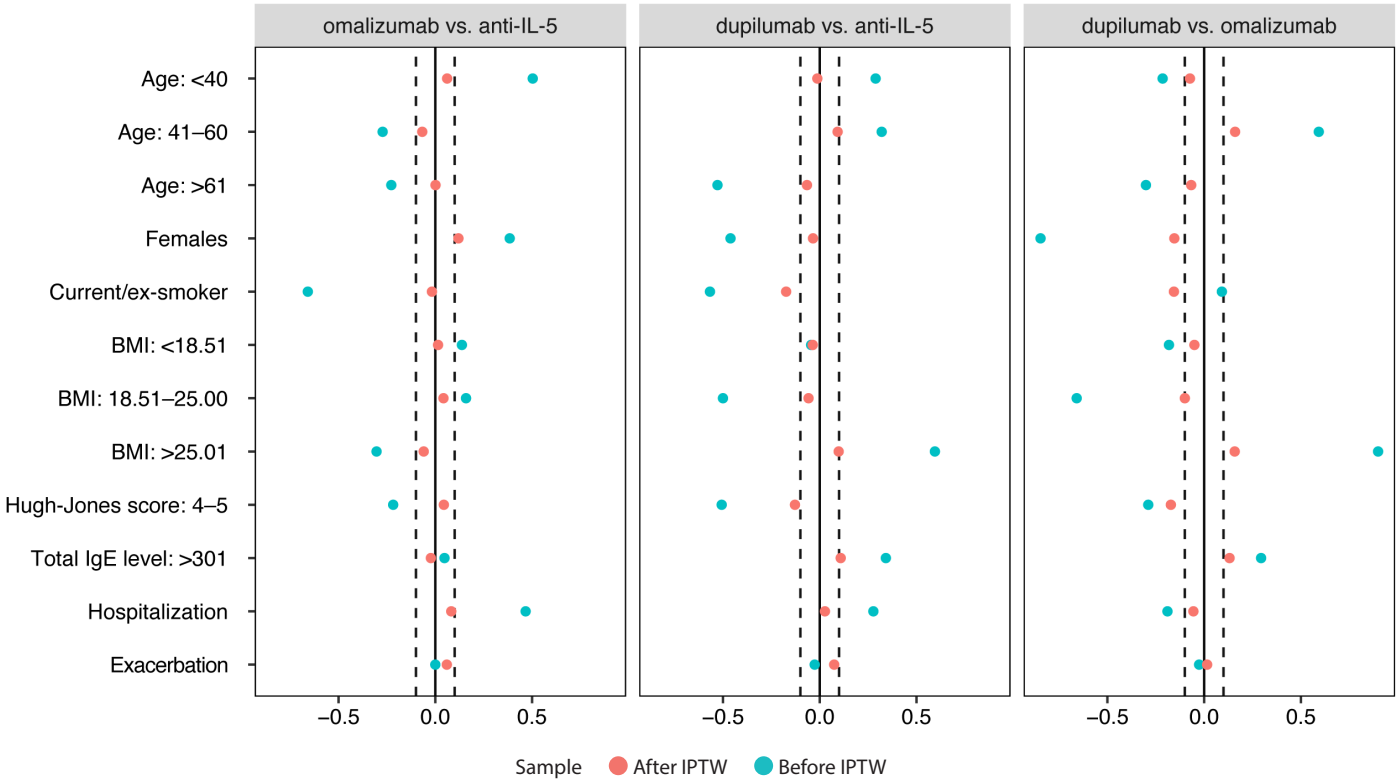

Figure S4. Standardized mean differences in baseline characteristics of the patients with asthma and an eosinophil count of ≥ 450/μL using asthma biologics, before and after ITPW.

IPTW, inverse probability treatment weighting; BMI, body mass index
The dotted line represents 0.1.

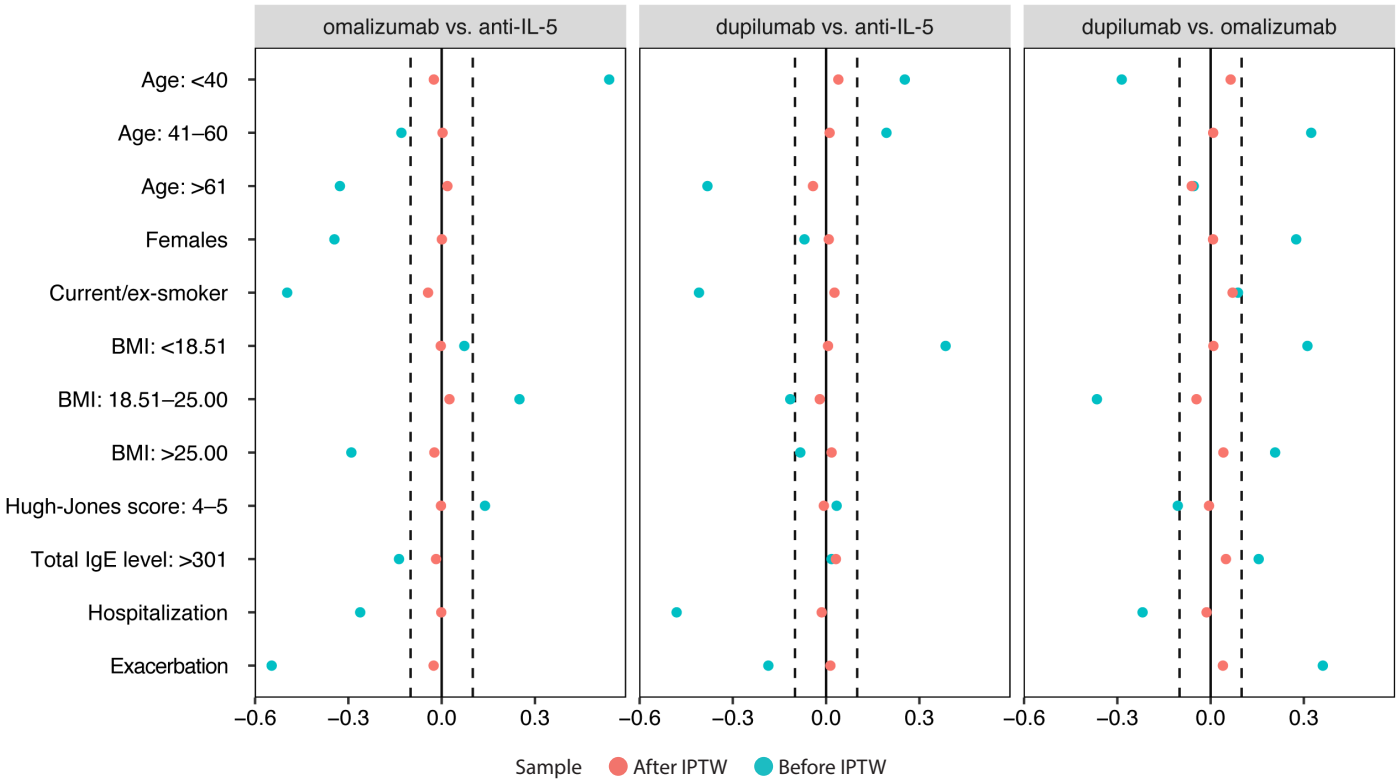

Figure S5. Standardized mean differences in baseline characteristics of the patients with asthma and an eosinophil count of < 450/μL using asthma biologics, before and after ITPW

IPTW, inverse probability treatment weighting; BMI, body mass index
The dotted line represents 0.1.