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Comparative analysis of biologics' effects on lung function parameters in severe asthma

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ABSTRACT

Background: Different biologics available as an add-on treatment for severe asthma (SA) demonstrated modest benefits on lung function parameters, but head-to-head comparisons are lacking.
Objective: To compare the effects of 4 biologics on lung function parameters (including small airways) at 6 and 12 months of treatment in patients with SA.
Methods: An observational multicenter study was conducted on adult patients with SA naive to biologics treated by benralizumab, dupilumab, mepolizumab, and omalizumab with lung function assessment by spirometry and gas dilution method at baseline, after 6 months (T6), and after 12 months of treatment.
Results: A total of 158 included patients were divided into the following 4 groups: 41 patients treated with omalizumab, 41 patients with mepolizumab, 36 patients with benralizumab, and 40 patients with dupilumab. Most lung function parameters were improved after 6 and 12 months of treatment without significant differences between groups except for the changes in the forced expiratory volume in 1 second in percentage (5.8 ± 15.2 vs 10.3 ± 10.8 vs 14.3 ± 15.3 vs 11.8 ± 14.6, $P = .025$) and forced vital capacity in percentage (3.0 ± 15.6 vs 6.7 ± 14.6 vs 13.6 ± 14.7 vs 8.4 ± 14.9, $P = .014$) at T6, which were higher in the group receiving benralizumab. Trends for greater effectiveness of dupilumab in improving small airway dysfunction and of benralizumab on distal airway obstruction were noted, but the results were not always significant.
Conclusion: All 4 biologics demonstrated comparable effectiveness in the improvement of lung function parameters after 6 and 12 months of treatment, except for the changes in the forced expiratory volume in 1 second and the forced vital capacity in percentage at T6, which were in favor of benralizumab.

Introduction

Severe asthma (SA), affecting 5% to 10% of patients with asthma, is characterized by poor symptom control and frequent exacerbations requiring systemic corticosteroids despite good adherence, adequate inhaler technique, and high intensity of treatment (medium/high doses of inhaled corticosteroids with a second controller or with maintenance of oral corticosteroids).[1] Recurrent exacerbations and type 2 inflammation in asthma are associated with airflow obstruction and accelerated lung function decline.[2-4]

Biologics targeting type 2 inflammation demonstrated undeniable benefits in SA outcomes by reducing exacerbations and the need for systemic corticosteroids and by improving symptom control.[1,4] An increase in lung function parameters has also been reported for these therapies by randomized clinical trials and real-world studies, probably due mostly to their effects on the inflammatory component of airway remodeling rather than a direct action on the anatomical structures.[5-8] Usually, lung function was assessed by standard parameter measurements without regard to small airway dysfunction (SAD), an important component of asthma that could be modified by biologics.[9-11] According to the results of real-world meta-analyses, after 1 year of treatment, omalizumab improved the forced expiratory volume in 1 second (FEV_1) by 0.25 L (95% CI: 0.03-0.48), mepolizumab by 0.17 L (95% CI: 0.11-0.24), benralizumab by 0.21 L (95% CI: 0.08-0.34), and dupilumab by 0.20 L (95% CI: −0.3 to 0.62), comparable to those reported by clinical trials.[5-7] However, head-to-head comparisons between biologics concerning their effect on lung function parameters, including the small airways, are lacking.

The aim of this study was to analyze, comparatively in real-world settings, the impact of 4 different biologics (benralizumab, dupilumab, mepolizumab, and omalizumab) on prebronchodilator lung

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function parameters assessed by spirometry and the gas dilution method after 6 and 12 months of treatment in adult patients with SA.

Methods

Study Design

An observational, multicenter, real-world study was performed using data from medical records of patients with SA according to the current definition,[1] treated by biologics, in the Departments of Pneumology of the Hospitals of Nancy (France), Saint-Luc, Brussels (Belgium), and San Martino, Genoa (Italy) from July 1, 2023, to March 31, 2024. The study was approved by each Institutional Ethical Committee (Institutional review board of the French learned society for respiratory medicine – Société de Pneumologie de Langue Française [CEPRO 2023-016], San Martino Hospital Ethical Committee [EC 2017, ID 3663], and UCLouvain Review Board [ref. 2006–121]). All patients provided written informed consent before extracting and using their data. All data were anonymized before analysis.

Patients

Inclusion criteria were adult patients with SA eligible for a biologic therapy and naive to such treatment. Clinical information on the patients was obtained from their medical folder and requested at the first visit in the Department of Pneumology. Key patient demographic data (eg, age, gender, body mass index, and smoking history) and prebiologic asthma clinical characteristics (eg, age of onset, comorbidities, exacerbation rate, level of control, biomarkers, and treatment) were collected (Table 1). Patients taking daily oral

Table 1
Descriptive Parameters of the Study Population at Baseline According to Treatment Group

Parameter	Group 1 Anti-IgE (n = 41)	Group 2 Anti–IL-5 (n = 41)	Group 3 Anti–IL-5R (n = 36)	Group 4 Anti–IL-4R (n = 40)	*P* value
Age, mean (SD)	51.07 (17.50)	54.34 (13.78)	56.97 (13.66)	52.90 (12.12)	.250
Female, n (%)	28 (68.29)	18 (43.90)	25 (69.44)	18 (45.00)	**.023**
BMI, mean (SD)	27.54 (4.62)	27.04 (4.59)	28.08 (5.05)	28.11 (5.39)	.782
Adult-onset asthma, n (%)	13 (31.71)	27 (65.85)	26 (72.22)	23 (57.50)	**.005**
Smoking history, n (%)					
Never-smoker	22 (53.66)	24 (58.54)	26 (72.22)	25 (62.50)	
Ex-smoker	18 (43.90)	16 (39.02)	10 (27.78)	14 (35.00)	.746
Active smoker	1 (2.44)	1 (2.44)	0 (0.00)	1 (2.50)	
Pack-years, mean (SD)	4.56 (6.13)	3.24 (4.60)	2.72 (5.12)	4.88 (7.29)	.439
Comorbidities, n (%)					
Allergic rhinitis	40 (97.56)	24 (58.54)	19 (52.77)	29 (72.50)	**<.001**
Nasal polyps	18 (43.90)	30 (73.17)	27 (75.00)	33 (82.50)	**.001**
Atopic dermatitis	7 (17.07)	5 (12.19)	3 (8.33)	6 (15.00)	.701
Dysfunctional breathing	8 (19.51)	3 (7.32)	1 (2.77)	7 (17.50)	.070
Obstructive sleep apnea	5 (12.19)	4 (9.76)	3 (8.33)	6 (15.00)	.805
Gastroesophageal reflux disease	20 (48.78)	23 (56.09)	15 (41.66)	19 (47.50)	.652
Obesity	12 (29.27)	10 (24.39)	11 (30.55)	11 (27.50)	.936
Psychological disorders	14 (34.15)	14 (34.15)	8 (22.22)	15 (37.50)	.513
Vocal cord dysfunction	0 (0.00)	0 (0.00)	0 (0.00)	2 (5.00)	.113
ACT score, mean (SD)	10.34 (3.53)	11.61 (4.68)	10.61 (3.97)	10.88 (3.52)	.671
Exacerbations/6 mo, mean (SD)	2.44 (1.27)	2.93 (1.59)	2.72 (0.97)	2.90 (1.35)	.220
Lung function, mean (SD)					
FEV_1 (L)	1.97 (0.67)	2.16 (0.79)	2.00 (0.67)	2.23 (0.76)	.493
FEV_1 (%)	71.54 (17.89)	74.12 (21.55)	73.11 (19.24)	72.83 (18.08)	.890
FVC (L)	3.13 (0.90)	3.32 (1.15)	3.01 (0.76)	3.40 (1.01)	.562
FVC (%)	94.88 (18.41)	93.63 (21.52)	93.22 (12.62)	90.28 (18.98)	.842
FEV_1/FVC (%)	62.90 (12.00)	64.60 (10.80)	64.40 (13.20)	65.70 (11.10)	.648
$FEF_{75\%}$ (L)	3.18 (1.69)	3.84 (1.81)	3.50 (1.90)	4.07 (2.13)	.169
$FEF_{75\%}$ (%)	51.32 (24.41)	59.44 (26.23)	58.00 (28.04)	61.95 (29.61)	.459
$FEF_{50\%}$ (L)	1.53 (1.05)	1.70 (0.95)	1.64 (0.94)	1.88 (1.23)	.532
$FEF_{50\%}$ (%)	37.29 (23.10)	41.20 (21.63)	41.50 (23.30)	45.98 (27.78)	.490
$FEF_{25\%}$ (L)	0.50 (0.42)	0.51 (0.39)	0.53 (0.35)	0.50 (0.32)	.694
$FEF_{25\%}$ (%)	30.00 (23.17)	32.66 (17.79)	36.33 (22.24)	38.60 (26.93)	.193
$FEF_{25\%-75\%}$ (L)	1.15 (0.84)	1.32 (0.80)	1.24 (0.77)	1.39 (0.87)	.492
$FEF_{25\%-75\%}$ (%)	33.39 (20.95)	37.39 (19.49)	38.92 (23.96)	43.15 (24.63)	.286
PEF (L/min)	314.40 (108.60)	329.40 (111.60)	329.60 (109.20)	362.40 (115.20)	.286
PEF (%)	75.24 (19.84)	74.93 (21.22)	79.58 (19.58)	79.78 (18.70)	.507
TLC (L)	5.70 (1.27)	5.94 (1.24)	5.86 (1.20)	5.91 (1.12)	.591
TLC (%)	106.66 (14.21)	103.24 (16.64)	107.03 (15.15)	99.70 (13.69)	.114
RV (L)	2.23 (0.96)	2.51 (0.95)	2.50 (0.91)	2.19 (0.64)	.162
RV (%)	119.02 (37.97)	124.76 (41.62)	127.17 (38.60)	115.95 (32.69)	.681
RV/TLC	39.24 (13.92)	41.85 (11.62)	42.43 (9.69)	39.75 (17.24)	.199
RV/TLC (%)	111.90 (24.41)	112.73 (23.64)	113.39 (21.97)	105.25 (32.46)	.452
Beta angle (°)	154.22 (18.66)	157.70 (19.11)	156.00 (17.29)	156.42 (18.02)	.710
$FEF_{50\%}$/PEF	0.28 (0.15)	0.31 (0.15)	0.29 (0.14)	0.30 (0.15)	.709
Total serum IgE, mean (SD) (UI/mL)	498.12 (614.14)	537.33 (442.61)	477.63 (481.42)	480.82 (864.68)	.392
BEC ($\times 10^9$/L), mean (SD)	0.812 (0.507)	0.731 (0.405)	0.927 (0.392)	0.587 (0.384)	.910
Long-term OCS, n (%)	4 (9.76)	10 (24.39)	7 (19.44)	4 (10.00)	.190
Daily OCS, mean mg/d (SD)	1.62 (5.56)	4.02 (8.08)	2.14 (5.69)	1.70 (5.27)	.147
ICS + LABA, n (%)	41 (100)	41 (100)	36 (100)	40 (100)	.997
LAMA, n (%)	30 (73.17)	36 (87.80)	34 (94.44)	38 (95.00)	.104

The p-values <0.05 (with statistical signficance) are put in bold.
Abbreviations: ACT, asthma control test; BEC, blood eosinophil count; BMI, body mass index (kg/m^2); $FEF_{75\%}$, forced expiratory flow at 75% of FVC; $FEF_{50\%}$, forced expiratory flow at 50% of FVC; $FEF_{25\%}$, forced expiratory flow at 25% of FVC; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; ICS, inhaled corticosteroid; IL-5, interleukin 5; IL-5R, interleukin 5 receptor; IL-4R, interleukin 4 receptor; LABA, long-acting β_2-agonist; LAMA, long-acting muscarinic antagonist; OCS, oral corticosteroid; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity.

corticosteroids for more than 30 days without interruption were considered "long-term" users. Each respiratory physician chose the biologics for his patients according to the individual clinical and biological criteria, but also the availability of these treatments in his country. The duration of a minimum of 12 months of treatment by the same biologic was mandatory for inclusion in the study. All included patients had a measurement of lung volumes by spirometry and gas dilution method at baseline when the biologic was started (T0), after 6 months (T6), and after 12 months of treatment (T12). Patients who refused collection of their medical data, those with stepdown of their controller medication during the 12-month follow-up, and/or those with incomplete information according to the study parameters were excluded. Adherence to the controller medication was assessed during the medical interview at each visit based on patient answers.

According to the chosen biologic, the patients were distributed into the following 4 different groups: group 1 was treated by anti-IgE antibody (omalizumab), group 2 by anti–IL-5 antibody (mepolizumab), group 3 by anti–IL-5R antibody (benralizumab), and group 4 by anti–IL-4R antibody (dupilumab).

End Points

The primary end point of this study was to compare the impact of 4 different biologics on prebronchodilator lung function parameters assessed by spirometry and gas dilution method (as absolute values and percentage of predicted) at 6 and 12 months of treatment in adult patients with SA. The technique of lung function parameters measurements and their interpretation were performed according to current guidelines.[12-14] Standard lung function parameters were recorded, including FEV_1, forced vital capacity (FVC), FEV_1/FVC, peak expiratory flow rate (PEF), total lung capacity (TLC), residual volume (RV), RV/TLC, flows at 25%, 50%, and 75% of the exhaled FVC, and forced expiratory flow (FEF) at 25% to 75% of FVC. The latter set of flows is considered to be more reproducible and more sensitive than FEV_1 to reflect the presence of SAD.[15,16] As obstruction in small airways leads to reduced flows at low lung volumes with a characteristic concave flow-volume curve even in the absence of proximal airway obstruction, we also comparatively analyzed the effect of the studied biologics on maximal expiratory flow-volume curves concavity

Table 2
Changes of Study Parameters From T0 to T6 and T12 for the Groups Treated by Anti-IgE and Anti–IL-4R Antibodies

Group	Lung function parameters mean (SD)	T0	T6	T12	*P* value T0 vs T6	*P* value T0 vs T12	*P* value T6 vs T12
Anti-IgE	FEV_1 (L)	1.97 (0.67)	2.16 (0.79)	2.25 (0.81)	**.011**	**.002**	.629
	FEV_1 (%)	71.54 (17.89)	77.37 (15.89)	80.63 (18.47)	**.019**	**.002**	.393
	FVC (L)	3.13 (0.90)	3.25 (0.97)	3.34 (1.01)	.100	**.031**	.683
	FVC (%)	94.88 (18.41)	97.93 (15.36)	101.39 (19.87)	.217	**.033**	.380
	FEV_1/FVC (%)	62.90 (12.00)	66.66 (11.70)	66.80 (12.50)	**.005**	**.004**	.928
	$FEF_{75\%}$ (L)	3.18 (1.69)	3.90 (2.28)	3.84 (2.08)	**.009**	**.017**	.901
	$FEF_{75\%}$ (%)	51.32 (24.41)	62.07 (31.13)	62.12 (28.95)	**.006**	**.006**	.994
	$FEF_{50\%}$ (L)	1.53 (1.05)	2.00 (1.24)	2.22 (1.37)	**.001**	**<.001**	.456
	$FEF_{50\%}$ (%)	37.29 (23.10)	46.88 (27.70)	51.54 (31.17)	**.003**	**<.001**	.477
	$FEF_{25\%}$ (L)	0.50 (0.42)	0.79 (0.83)	0.79 (0.67)	**.010**	**.002**	.997
	$FEF_{25\%}$ (%)	30.00 (23.17)	44.07 (41.66)	47.34 (41.21)	**.006**	**.002**	.722
	$FEF_{25\%-75\%}$ (L)	1.15 (0.84)	1.50 (1.08)	1.54 (1.09)	**.024**	**.012**	.861
	$FEF_{25\%-75\%}$ (%)	33.39 (20.95)	41.49 (25.55)	43.76 (26.53)	**.023**	**.006**	.694
	PEF (L/min)	314.40 (108.60)	342.30 (118.20)	350.40 (117.00)	**.023**	**.011**	.743
	PEF (%)	75.24 (19.84)	81.88 (18.55)	83.68 (19.88)	**.014**	**.008**	.672
	TLC (L)	5.70 (1.27)	5.67 (1.06)	5.74 (1.23)	.670	.613	.779
	TLC (%)	106.66 (14.21)	106.66 (14.06)	107.76 (16.41)	1.000	.450	.746
	RV (L)	2.23 (0.96)	2.19 (0.74)	2.29 (0.81)	.623	.498	.550
	RV (%)	119.02 (37.97)	118.61 (35.28)	124.07 (37.07)	.910	.297	.496
	RV/TLC	39.24 (13.92)	39.22 (13.34)	40.39 (12.30)	.976	.291	.681
	RV/TLC (%)	111.90 (24.41)	106.54 (24.24)	108.80 (24.34)	.092	.417	.674
	Beta angle (°)	154.22 (18.66)	161.77 (21.71)	164.98 (24.52)	**<.001**	**<.001**	.533
	$FEF_{50\%}$/PEF	0.28 (0.15)	0.34 (0.18)	0.38 (0.21)	**.010**	**<.001**	.453
Anti–IL-4R	FEV_1 (L)	2.23 (0.76)	2.61 (0.86)	2.67 (0.83)	**<.001**	**<.001**	.736
	FEV_1 (%)	72.83 (18.08)	84.63 (18.84)	86.83 (18.08)	**<.001**	**<.001**	.596
	FVC (L)	3.40 (1.01)	3.72 (0.98)	3.73 (0.98)	**<.001**	**<.001**	.976
	FVC (%)	90.28 (18.98)	98.68 (18.10)	95.83 (22.39)	**.001**	.139	.533
	FEV_1/FVC (%)	65.70 (11.10)	67.50 (10.00)	71.00 (9.20)	**.001**	**<.001**	.486
	$FEF_{75\%}$ (L)	4.07 (2.13)	5.02 (2.28)	5.21 (2.29)	**<.001**	**<.001**	.708
	$FEF_{75\%}$ (%)	61.95 (29.61)	75.60 (28.94)	78.75 (28.85)	**<.001**	**<.001**	.627
	$FEF_{50\%}$ (L)	1.88 (1.23)	2.48 (1.47)	2.67 (1.39)	**<.001**	**<.001**	.557
	$FEF_{50\%}$ (%)	45.98 (27.78)	59.65 (31.09)	66.66 (31.86)	**.001**	**<.001**	.327
	$FEF_{25\%}$ (L)	0.50 (0.32)	0.70 (0.45)	0.75 (0.41)	**.001**	**<.001**	.617
	$FEF_{25\%}$ (%)	38.60 (26.93)	53.30 (33.39)	58.78 (30.72)	**.013**	**<.001**	.448
	$FEF_{25\%-75\%}$ (L)	1.39 (0.87)	1.88 (1.08)	2.00 (1.06)	**<.001**	**<.001**	.605
	$FEF_{25\%-75\%}$ (%)	43.15 (24.63)	57.70 (28.23)	61.60 (30.22)	**<.001**	**<.001**	.553
	PEF (L/min)	362.40 (115.20)	410.40 (119.80)	403.08 (120.60)	**<.001**	**.006**	.799
	PEF (%)	79.78 (18.70)	90.30 (18.04)	88.78 (16.63)	**<.001**	**.003**	.695
	TLC (L)	5.91 (1.12)	5.94 (1.11)	5.86 (1.11)	.664	.572	.753
	TLC (%)	99.70 (13.69)	100.28 (13.64)	99.53 (14.23)	.694	.909	.810
	RV (L)	2.19 (0.64)	2.27 (0.77)	2.20 (0.73)	.281	.942	.683
	RV (%)	115.95 (32.69)	115.23 (37.25)	113.43 (35.67)	.855	.565	.826
	RV/TLC	39.75 (17.24)	37.75 (11.47)	37.43 (11.07)	.413	.371	.898
	RV/TLC (%)	105.25 (32.46)	105.80 (30.12)	105.63 (29.69)	.887	.920	.979
	Beta angle (°)	156.42 (18.02)	163.05 (17.85)	167.52 (17.99)	**.002**	**<.001**	.268
	$FEF_{50\%}$/PEF	0.30 (0.15)	0.35 (0.15)	0.39 (0.20)	**.004**	**<.001**	.258

The p-values <0.05 (with statistical signficance) are put in bold.
Abbreviations: $FEF_{75\%}$, forced expiratory flow at 75% of FVC; $FEF_{50\%}$, forced expiratory flow at 50% of FVC; $FEF_{25\%}$, forced expiratory flow at 25% of FVC; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IL-4R, interleukin 4 receptor; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity; T0, baseline; T6, 6 months; T12, 12 months.

assessed by β−angle and $FEF_{50\%}$/PEF.[17] β-angle reflects the curvature around the middle of the FEF−volume loop slope and is calculated by the following formula: $\beta = 180 - \tan^{-1}[(PEF - FEF_{50\%}) / (0.5 \times FVC)] + \tan^{-1}[FEF_{50\%} / (0.5 \times FVC)]$. The value of β-angle inferior to 180° is associated with upward concavity of the maximal expiratory flow-volume curves.[18] A simplified approach to estimating β−angle is $FEF_{50\%}$/PEF, with values less than 0.5 indicating upward concavity of the flow-volume curve.[17,19] The secondary end point of the study was the comparison of the response to treatment between groups at T6 and T12, defined as an increase of more than 10% of FEV_1 compared with baseline, a cutoff currently considered as a clinically meaningful change.[14]

Statistical Analysis

Statistical analysis was performed using the SPPS program (SAS Institute, Cary, North Carolina). Quantitative variables are expressed as mean values with SD. Categorial variables are stated as numbers and percentages. Comparisons between groups were performed using an analysis of variance (ANOVA) test and the Tukey-Kramer procedure for normal distribution of variables or Kruskal−Wallis's test if the distribution was not normal. Comparisons of values between T0 vs T6, T0 vs T12, and T6 vs T12 were performed using the *t* test for normally distributed continuous variables and rank sum tests for non-normally distributed continuous variables.

For the assessment of response to biologics, the changes between T6 and T0 (Δ = T6-T0 values), respectively T12 and T0 (Δ = T12-T0 values) of the parameters studied, were compared using the ANOVA method. Patient age, sex at time of birth, height, smoking status, body mass index, prebiologic exacerbation rate, baseline eosinophil count, and daily oral corticosteroid use were included as covariates. In all post hoc ANOVA analyses, adjustments for multiple testing were applied to reduce the risk of type I errors.

Table 3
Comparison of Study Parameters at T6 and T12 vs T0 for the Groups Treated by Anti−IL-5 and Anti−IL-5R Antibodies

Group	Lung function parameters mean (SD)	T0	T6	T12	*P* value T0 vs T6	*P* value T0 vs T12	*P* value T6 vs T12
Anti−IL-5	FEV_1 (L)	2.16 (0.79)	2.46 (0.85)	2.55 (0.89)	**<.001**	**<.001**	.607
	FEV_1 (%)	74.12 (21.55)	84.41 (22.77)	86.88 (20.77)	**<.001**	**<.001**	.610
	FVC (L)	3.32 (1.15)	3.54 (1.03)	3.71 (1.06)	**.010**	**<.001**	.480
	FVC (%)	93.63 (21.52)	100.34 (20.93)	103.10 (18.64)	**.005**	**<.001**	.531
	FEV_1/FVC	64.60 (10.80)	68.80 (12.50)	68.40 (11.50)	**.002**	**.003**	.898
	$FEF_{75\%}$ (L)	3.84 (1.81)	4.45 (1.89)	4.62 (2.05)	**.006**	**.003**	.692
	$FEF_{75\%}$ (%)	59.44 (26.23)	69.41 (27.64)	72.46 (28.62)	**.004**	**.001**	.625
	$FEF_{50\%}$ (L)	1.70 (0.95)	2.19 (1.11)	2.32 (1.27)	**<.001**	**<.001**	.625
	$FEF_{50\%}$ (%)	41.20 (21.63)	54.05 (26.20)	60.56 (32.47)	**<.001**	**<.001**	.321
	$FEF_{25\%}$ (L)	0.51 (0.39)	0.73 (0.68)	0.72 (0.63)	**.018**	**.023**	.935
	$FEF_{25\%}$ (%)	32.66 (17.79)	47.93 (36.20)	53.20 (38.46)	**.006**	**<.001**	.525
	$FEF_{25\%-75\%}$ (L)	1.32 (0.80)	1.57 (0.90)	1.58 (0.95)	**.006**	**.004**	.924
	$FEF_{25\%-75\%}$ (%)	37.39 (19.49)	44.76 (22.06)	47.17 (23.07)	**.005**	**<.001**	.630
	PEF (L/min)	329.40 (111.60)	388.20 (127.20)	394.20 (133.20)	**<.001**	**<.001**	.839
	PEF (%)	74.93 (21.22)	88.07 (21.36)	88.22 (21.93)	**<.001**	**<.001**	.976
	TLC (L)	5.94 (1.24)	5.96 (1.35)	5.99 (1.34)	.897	.657	.916
	TLC (%)	103.24 (16.64)	103.29 (17.49)	103.00 (17.73)	.971	.869	.940
	RV (L)	2.51 (0.95)	2.36 (0.90)	2.34 (0.89)	.133	.103	.926
	RV (%)	124.76 (41.62)	116.73 (38.29)	115.68 (39.76)	.086	.060	.903
	RV/TLC	41.85 (11.62)	39.07 (9.74)	39.95 (9.90)	**.014**	.251	.687
	RV/TLC (%)	112.73 (23.64)	108.59 (24.19)	106.46 (27.44)	.073	**.046**	.711
	Beta angle (°)	157.70 (19.11)	161.45 (18.34)	163.07 (19.10)	.097	**.032**	.696
	$FEF_{50\%}$/PEF	0.31 (0.15)	0.34 (0.05)	0.35 (0.25)	.123	**.045**	.703
Anti−IL-5R	FEV_1 (L)	2.00 (0.67)	2.32 (0.69)	2.36 (0.69)	**<.001**	**<.001**	.830
	FEV_1 (%)	73.11 (19.24)	87.44 (20.55)	89.64 (20.02)	**<.001**	**<.001**	.648
	FVC (L)	3.01 (0.76)	3.39 (0.90)	3.41 (1.01)	**<.001**	**<.001**	.932
	FVC (%)	93.22 (12.62)	106.86 (18.89)	107.33 (22.21)	**<.001**	**<.001**	.923
	FEV_1/FVC	64.40 (13.20)	67.60 (9.90)	69.00 (10.80)	**.004**	**.002**	.658
	$FEF_{75\%}$ (L)	3.50 (1.90)	4.31 (1.85)	4.31 (1.82)	**.002**	**.001**	.985
	$FEF_{75\%}$ (%)	58.00 (28.04)	71.78 (29.50)	73.08 (30.03)	**.001**	**<.001**	.853
	$FEF_{50\%}$ (L)	1.64 (0.94)	2.21 (1.17)	2.39 (1.20)	**<.001**	**<.001**	.514
	$FEF_{50\%}$ (%)	41.50 (23.30)	55.22 (26.91)	60.17 (26.55)	**<.001**	**<.001**	.435
	$FEF_{25\%}$ (L)	0.53 (0.35)	0.93 (1.14)	0.79 (0.55)	**.047**	**.005**	.513
	$FEF_{25\%}$ (%)	36.33 (22.24)	49.50 (32.64)	57.19 (38.58)	**.011**	**<.001**	.364
	$FEF_{25\%-75\%}$ (L)	1.24 (0.77)	1.54 (0.79)	1.67 (0.81)	**<.001**	**<.001**	.490
	$FEF_{25\%-75\%}$ (%)	38.92 (23.96)	49.86 (24.25)	54.72 (28.87)	**.001**	**<.001**	.442
	PEF (L/min)	329.60 (109.20)	367.80 (112.20)	368.40 (118.40)	**.006**	**.005**	.990
	PEF (%)	79.58 (19.58)	90.36 (22.54)	90.89 (24.94)	**.005**	**.002**	.925
	TLC (L)	5.86 (1.20)	5.87 (1.13)	5.91 (1.15)	.920	.584	.870
	TLC (%)	107.03 (15.15)	107.47 (14.77)	108.28 (16.49)	.756	.430	.828
	RV (L)	2.50 (0.91)	2.34 (0.73)	2.38 (0.82)	.068	.262	.833
	RV (%)	127.17 (38.60)	118.06 (33.45)	119.56 (39.54)	**.034**	.197	.863
	RV/TLC	42.43 (9.69)	39.96 (9.40)	40.31 (10.68)	**.013**	.113	.885
	RV/TLC (%)	113.39 (21.97)	105.83 (20.87)	105.42 (23.34)	**.004**	**.038**	.937
	Beta angle (°)	156.00 (17.29)	163.60 (16.62)	168.72 (21.06)	**<.001**	**<.001**	.256
	$FEF_{50\%}$/PEF	0.29 (0.14)	0.35 (0.14)	0.40 (0.28)	**.001**	**<.001**	.255

The p-values <0.05 (with statistical signficance) are put in bold.
Abbreviations: $FEF_{75\%}$, forced expiratory flow at 75% of FVC; $FEF_{50\%}$, forced expiratory flow at 50% of FVC; $FEF_{25\%}$, forced expiratory flow at 25% of FVC; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IL-5, interleukin 5; IL-5R, interleukin 5 receptor; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity; T0, baseline; T6, 6 months; T12, 12 months.

Multivariate logistic regression was performed to assess the predictive factors associated with a response to treatment for all groups. Statistical significance was set at *P* values less than .05.

Results

Patients' Characteristics

A total of 158 biologic-naive patients with SA eligible for such treatment with a mean age of 53 ± 12 years were included in the study and divided into 4 groups according to the chosen biologic (Table 1). There was a significant difference between the groups concerning the gender of patients, with more women (approximately 70% of patients) in the groups treated by anti-IgE and anti–IL-5R antibodies compared with the others ($P = .023$). The prevalence of adult-onset asthma was lower in the anti-IgE group (31.7%) than in the other groups (more than half of the patients) ($P = .005$). The groups were comparable in terms of smoking status (with a predominance of never-smoker patients in all groups) and tobacco consumption, exacerbation rate, asthma control test score, biomarkers (blood eosinophil count and serum IgE level), and controller medication (oral corticosteroids use included) (Table 1). The number of exacerbations at T0 was 2.8 ± 1.3 per 6 months in the study population, and the mean asthma control test score was 10.9 ± 4.0 points, confirming the criteria for SA. The patients were overweight, with a body mass index of 27.7 ± 4.9 kg/m^2 without differences between groups. Regarding the distribution of asthma comorbidities, almost all patients receiving omalizumab had allergic rhinitis, compared with more than half of those treated by mepolizumab and benralizumab ($P < .001$), whereas nasal polyps were more prevalent in the groups treated with anti–IL-5, –IL-5R, and –IL-4R antibodies (73.2%-82.5% of patients) vs the anti-IgE group (43.9% of patients) ($P = .001$). No differences were registered for the other comorbidities.

Concerning the lung function parameters, at T0, in the study population, the mean values in percent of predicted were 72.9% ± 19.1% for FEV_1, 93.0% ± 18.2% for FVC, 104.1% ± 15.1% for TLC, 121.6% ± 37.8% for RV, 38.2% ± 22.4% for $FEF_{25\%-75\%}$, and 57.6% ± 27.1% for $FEF_{75\%}$. The airflow obstruction was proved by the FEV_1/FVC of 64.0% ± 12.0%, whereas the upward concavity of the flow-volume curve was demonstrated by the β-angle mean value of 156.1 ± 18.2° and the $FEF_{50\%}$/PEF of 0.3 ± 0.2. There were no significant differences between groups regarding the lung function parameters at T0 (Table 1).

Primary Outcomes

Almost all the study parameters were significantly improved by the treatment (except TLC), without differences between the results at T6 and T12 (Tables 2 and 3). The improvement of the FVC was significant after 6 and 12 months of treatment compared with baseline for the anti–IL-5 and anti–IL-5R groups, but only at T12 for the anti-IgE group and at T6 for the anti–IL-4R group. There was no change in the RV during the study except for the predicted value at T6, which was significantly lower in the group treated by the anti–IL-5R antibody compared with the others. The β-angle and the $FEF_{50\%}$/PEF were improved for all the groups, but the result did not reach significance for the anti–IL-5 group at T6 (Table 3). The changes in several study parameters (FEV_1, FEV_1/FVC, $FEF_{75\%}$, $FEF_{25\%-75\%}$, β-angle, and $FEF_{50\%}$/PEF) from baseline to T12 are represented in Figure 1.

The comparative analyses between groups at T6 and T12 revealed similar results for almost all lung function parameters. Only 3 significant differences were found in favor of the anti–IL-4R group compared with the others, with higher values for $FEF_{25\%-75\%}$ (percentage of predicted) at T6 and T12 and for $FEF_{75\%}$ (L) at T12 (Table 4). Regarding the changes in outcome parameters, the effect of biologics was comparable at T6 and T12, except that the ΔFEV_1 and ΔFVC (%) were significantly higher in the anti–IL-5R group vs the others at T6 (Table 5).

Secondary Outcomes

Concerning the response to treatment defined as an increase in FEV_1 by more than 10% from baseline, at T6, the proportion of responders was 37% in the anti-IgE group, 54% in the anti–IL-5 group, 56% in the anti–IL-5R group, and 45% in the anti–IL-4R group ($P = .013$). Similarly, at T12, the rate of responders was significantly lower in the anti-IgE group (46%) than in the other groups (66% in the

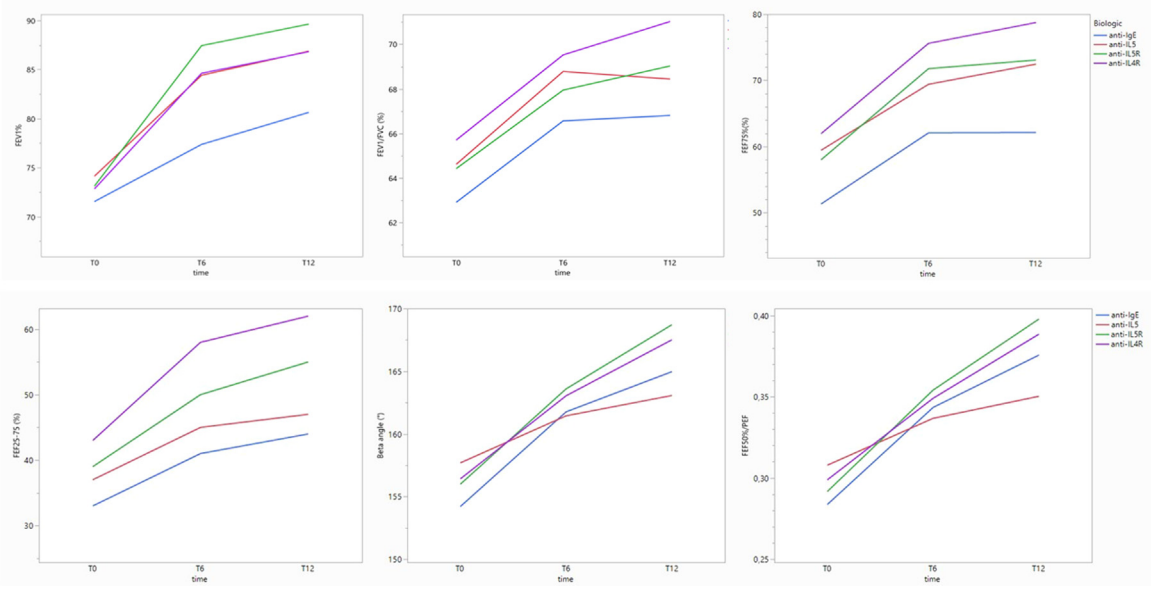

Figure 1. Changes of several lung function parameters from baseline to 12 months in all groups. Anti-IgE, anti–IgE antibody; anti–IL-5, anti–interleukin 5 antibody; anti–IL-5R, anti–interleukin 5 receptor antibody; anti–IL-4R, anti–interleukin 4 receptor antibody; $FEF_{75\%}$, forced expiratory flow at 75% of FVC; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of FVC; $FEF_{50\%}$, forced expiratory flow at 50% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; PEF, peak expiratory flow; T0, at baseline; T6, after 6 months; T12, after 12 months.

Table 4
Comparison of Study Parameters at T6 and T12 of Treatment Between Groups

Lung function parameters mean (SD)	Group 1 Anti-IgE n = 41	Group 2 Anti–IL-5 n = 41	Group 3 Anti–IL-5R n = 36	Group 4 Anti–IL-4R n = 40	*P* value
At T6					
FEV1 (L)	2.16 (0.79)	2.46 (0.85)	2.32 (0.69)	2.61 (0.86)	.120
FEV1 (%)	77.37 (15.89)	84.41 (22.77)	87.44 (20.55)	84.63 (18.84)	.074
FVC (L)	3.25 (0.97)	3.54 (1.03)	3.39 (0.90)	3.72 (0.98)	.233
FVC (%)	97.93 (15.36)	100.34 (20.93)	106.86 (18.89)	98.68 (18.10)	.103
FEV1/FVC (%)	66.66 (11.70)	68.80 (12.50)	67.90 (9.90)	67.50 (10.00)	.674
$FEF_{75\%}$ (L)	3.90 (2.28)	4.45 (1.89)	4.31 (1.85)	5.02 (2.28)	.103
$FEF_{75\%}$ (%)	62.90 (12.00)	69.41 (27.64)	71.78 (29.50)	75.60 (28.94)	.133
$FEF_{50\%}$ (L)	2.00 (1.24)	2.19 (1.11)	2.21 (1.17)	2.48 (1.47)	.484
$FEF_{50\%}$ (%)	46.88 (27.70)	54.05 (26.20)	55.22 (26.91)	59.65 (31.09)	.212
$FEF_{25\%}$ (L)	0.79 (0.83)	0.73 (0.68)	0.93 (1.14)	0.70 (0.45)	.521
$FEF_{25\%}$ (%)	44.07 (41.66)	47.93 (36.20)	49.50 (32.64)	53.30 (33.39)	.188
$FEF_{25\%-75\%}$ (L)	1.50 (1.08)	1.57 (0.90)	1.54 (0.79)	1.88 (1.08)	.247
$FEF_{25\%-75\%}$ (%)	41.49 (25.55)	44.76 (22.06)	49.86 (24.25)	57.70 (28.23)	**.035**
PEF (L/min)	342.30 (118.20)	388.20 (127.20)	367.80 (112.30)	410.40 (119.80)	.076
PEF (%)	81.88 (18.55)	88.07 (21.36)	90.36 (22.54)	90.30 (18.04)	.153
TLC (L)	5.70 (1.27)	5.96 (1.35)	5.87 (1.13)	5.94 (1.11)	.692
TLC (%)	106.66 (14.21)	103.29 (17.49)	107.47 (14.77)	100.28 (13.64)	.125
RV (L)	2.19 (0.74)	2.36 (0.90)	2.34 (0.73)	2.27 (0.77)	.769
RV (%)	118.61 (35.28)	116.73 (38.29)	118.06 (33.45)	115.23 (37.25)	.948
RV/TLC	39.22 (13.34)	39.07 (9.74)	39.96 (9.40)	37.75 (11.47)	.807
RV/TLC (%)	106.54 (24.24)	108.59 (24.19)	105.83 (20.87)	105.80 (30.12)	.977
Beta angle (°)	161.77 (21.71)	161.45 (18.34)	163.60 (16.62)	163.05 (17.85)	.886
$FEF_{50\%}$/PEF	0.34 (0.18)	0.34 (0.05)	0.35 (0.14)	0.35 (0.15)	.881
At T12					
FEV1 (L)	2.25 (0.81)	2.55 (0.89)	2.36 (0.69)	2.67 (0.83)	.116
FEV1 (%)	80.63 (18.47)	86.88 (20.77)	89.64 (20.02)	86.83 (18.08)	.166
FVC (L)	3.34 (1.01)	3.71 (1.06)	3.41 (1.01)	3.73 (0.98)	.217
FVC (%)	101.39 (19.87)	103.10 (18.64)	107.33 (22.21)	95.83 (22.39)	.189
FEV1/FVC (%)	66.80 (12.50)	68.40 (11.50)	69.00 (10.80)	71.00 (9.20)	.518
$FEF_{75\%}$ (L)	3.84 (2.08)	4.62 (2.05)	4.31 (1.82)	5.21 (2.29)	**.035**
$FEF_{75\%}$ (%)	62.12 (28.95)	72.46 (28.62)	73.08 (30.03)	78.75 (28.85)	.057
$FEF_{50\%}$ (L)	2.22 (1.37)	2.32 (1.27)	2.39 (1.20)	2.67 (1.39)	.470
$FEF_{50\%}$ (%)	51.54 (31.17)	60.56 (32.47)	60.17 (26.55)	66.66 (31.86)	.129
$FEF_{25\%}$ (L)	0.79 (0.67)	0.72 (0.63)	0.79 (0.55)	0.75 (0.41)	.529
$FEF_{25\%}$ (%)	47.34 (41.21)	53.20 (38.46)	57.19 (38.58)	58.78 (30.72)	.087
$FEF_{25\%-75\%}$ (L)	1.54 (1.09)	1.58 (0.95)	1.67 (0.81)	2.00 (1.06)	.111
$FEF_{25\%-75\%}$ (%)	43.76 (26.53)	47.17 (23.07)	54.72 (28.87)	61.60 (30.22)	**.022**
PEF (L/min)	350.40 (117.00)	394.20 (133.30)	368.40 (118.40)	403.08 (120.70)	.228
PEF (%)	83.68 (19.88)	88.22 (21.93)	90.89 (24.94)	88.78 (16.63)	.523
TLC (L)	5.74 (1.23)	5.99 (1.34)	5.91 (1.15)	5.86 (1.11)	.755
TLC (%)	107.76 (16.41)	103.00 (17.73)	108.28 (16.49)	99.53 (14.23)	.065
RV (L)	2.29 (0.81)	2.34 (0.89)	2.38 (0.82)	2.20 (0.73)	.873
RV (%)	124.07 (37.07)	115.68 (39.76)	119.56 (39.54)	113.43 (35.67)	.605
RV/TLC	40.39 (12.30)	39.95 (9.90)	40.31 (10.68)	37.43 (11.07)	.762
RV/TLC (%)	108.80 (24.34)	106.46 (27.44)	105.42 (23.34)	105.63 (29.69)	.946
Beta angle (°)	164.98 (24.52)	163.07 (19.10)	168.72 (21.06)	167.52 (17.99)	.516
$FEF_{50\%}$/PEF	0.38 (0.21)	0.35 (0.25)	0.40 (0.28)	0.39 (0.20)	.562

The p-values <0.05 (with statistical signficance) are put in bold.
Abbreviations: $FEF_{75\%}$, forced expiratory flow at 75% of FVC; $FEF_{50\%}$, forced expiratory flow at 50% of FVC; $FEF_{25\%}$, forced expiratory flow at 25% of FVC; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IL-4R, interleukin 4 receptor; IL-5, interleukin 5; IL-5R, interleukin 5 receptor; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity; T6, 6 months; T12, 12 months.

anti–IL-5 group, 67% in the anti–IL-5R group, and 65% in the anti–IL-4R group) ($P = .002$). The rates of responders were significantly higher for all biologics at T12 compared with T6 (all $P < .001$). These results are represented in Figure 2. As a predictive factor for a response to treatment, the presence of nasal polyps was associated with greater chances of response with an odds ratio of 4.50 (95% CI: 1.16-17.51) in the anti-IgE group, 9.00 (95% CI: 1.63-19.76) in the anti–IL-5 group, 7.00 (95% CI: 1.20-10.83) in the anti–IL-5R group, and 11.11 (95% CI: 0.21-15.76) in the anti–IL-4R group (all $P < .03$) (Table 6).

Discussion

This study investigated the effect of benralizumab, dupilumab, mepolizumab, and omalizumab on lung function parameters (SAD included) in biologic-naive patients with SA in a real-world setting and found similar effectiveness of these biologics after 6 and 12 months of treatment.

Most previous real-world studies assessing the effectiveness of biologics in SA focused on reducing exacerbation rates, asthma control, and systemic corticosteroid-sparing effects. The FEV_1 was rarely the primary objective.[6,7] In our study, FEV_1 improvement in the anti-IgE group was similar to those reported in a large meta-analysis including real-world studies: 0.20 ± 0.47 L vs 0.22 [95% CI: 0.09-0.36] L at T6, respectively, 0.28 ± 0.53 L vs 0.25 [95% CI: 0.03-0.48] L at T12.[6] In contrast, FEV_1 changes in the other groups were greater than those previously found in real-world setting.[7] At T12, FEV_1 increased by 0.39 ± 0.40L in the anti–IL-5 group in this study vs 0.21 ± 0.46 L reported in the REDES cohort.[20] Similarly, FEV_1 was improved at T12 by 0.36 ± 0.42 L in this study in the anti–IL-5R group vs 0.27 [95% CI: 0.20-0.34] L found in the XALOC-1 cohort and by 0.44 ± 0.49 L in the anti–IL-4R group vs 0.30 [95% CI: 0.19-0.34] L in a Dutch cohort.[21,22] FEV_1 trajectories analysis for all biologics revealed a sustained

Table 5
Changes (Δ) in Outcomes Parameters at T6 and T12 Compared With T0 for All Groups

Lung function parameters mean (SD)	Group 1 Anti-IgE n = 41	Group 2 Anti–IL-5 n = 41	Group 3 Anti–IL-5R n = 36	Group 4 Anti–IL-4R n = 40	*P* value
Δ T6 – T0					
Δ FEV_1 (L)	0.20 (0.47)	0.29 (0.37)	0.32 (0.40)	0.38 (0.51)	.075
Δ FEV_1 (%)	5.83 (15.24)	10.29 (10.61)	14.33 (15.29)	11.80 (14.59)	**.025**
Δ FVC (L)	0.12 (0.47)	0.22 (0.53)	0.33 (0.47)	0.32 (0.51)	.171
Δ FVC (%)	3.05 (15.57)	6.71 (14.59)	13.64 (14.70)	8.40 (14.96)	**.014**
Δ FEV_1/FVC (%)	3.66 (7.81)	4.17 (7.90)	3.53 (6.85)	3.83 (6.94)	.816
Δ $FEF_{75\%}$ (L)	0.72 (1.69)	0.61 (1.34)	0.80 (1.44)	0.95 (1.38)	.391
Δ $FEF_{75\%}$ (%)	10.75 (23.53)	9.97 (21.11)	13.77 (23.01)	13.65 (18.21)	.430
Δ $FEF_{50\%}$ (L)	0.48 (0.88)	0.49 (0.66)	0.57 (0.70)	0.60 (0.91)	.350
Δ $FEF_{50\%}$ (%)	9.58 (19.26)	12.85 (17.32)	13.72 (17.18)	13.67 (24.70)	.175
Δ $FEF_{25\%}$ (L)	0.29 (0.70)	0.22 (0.57)	0.39 (1.15)	0.20 (0.37)	.957
Δ $FEF_{25\%}$ (%)	14.07 (30.86)	15.27 (33.74)	13.16 (29.54)	14.70 (35.66)	.970
Δ $FEF_{25\%-75\%}$ (L)	0.35 (0.96)	0.25 (0.55)	0.30 (0.47)	0.49 (0.77)	.738
Δ $FEF_{25\%-75\%}$ (%)	8.10 (21.84)	7.37 (15.86)	10.94 (18.53)	14.55 (21.69)	.582
Δ PEF (L/min)	27.90 (11.40)	58.70 (10.20)	38.80 (13.00)	48.10 (12.00)	.156
Δ PEF (%)	6.63 (16.49)	13.15 (12.66)	10.77 (19.44)	10.53 (17.04)	.091
Δ TLC (L)	0.03 (0.44)	0.01 (0.55)	0.01 (0.51)	0.03 (0.48)	.755
Δ TLC (%)	0.00 (6.65)	0.05 (8.59)	0.44 (8.51)	0.57 (9.17)	.966
Δ RV (L)	−0.04 (0.52)	−0.15 (0.64)	−0.16 (0.53)	0.07 (0.43)	.150
Δ RV (%)	−0.41 (23.34)	−8.02 (29.21)	−9.11 (24.77)	−0.73 (24.89)	.222
Δ RV/TLC	−0.02 (5.13)	−2.78 (6.89)	−2.46 (5.64)	−2.00 (15.28)	.083
Δ RV/TLC (%)	−5.37 (19.91)	−4.15 (14.41)	−7.55 (14.51)	0.55 (24.23)	.291
Δ Beta angle (°)	7.56 (11.97)	3.75 (14.12)	7.61 (12.24)	6.63 (12.26)	.705
Δ $FEF_{50\%}$/PEF	0.06 (0.11)	0.03 (0.12)	0.06 (0.11)	0.05 (0.10)	.570
Δ T12 – T0					
Δ FEV_1 (L)	0.28 (0.53)	0.39 (0.40)	0.36 (0.42)	0.44 (0.49)	.153
Δ FEV_1 (%)	9.09 (17.53)	12.76 (10.97)	16.53 (15.46)	14.00 (14.04)	.064
Δ FVC (L)	0.21 (0.61)	0.39 (0.46)	0.35 (0.57)	0.33 (0.50)	.210
Δ FVC (%)	6.51 (18.83)	9.46 (11.42)	14.11 (18.03)	5.55 (23.26)	.083
Δ FEV_1/FVC (%)	3.90 (8.05)	3.82 (7.74)	4.61 (8.02)	5.33 (7.62)	.508
Δ $FEF_{75\%}$ (L)	0.66 (1.71)	0.78 (1.60)	0.81 (1.38)	1.14 (1.53)	.234
Δ $FEF_{75\%}$ (%)	10.80 (23.97)	13.02 (24.34)	15.08 (23.26)	16.80 (20.00)	.303
Δ $FEF_{50\%}$ (L)	0.69 (1.04)	0.62 (0.75)	0.75 (0.86)	0.79 (0.87)	.522
Δ $FEF_{50\%}$ (%)	14.24 (21.76)	19.37 (18.73)	18.67 (19.77)	20.63 (24.60)	.334
Δ $FEF_{25\%}$ (L)	0.29 (0.57)	0.21 (0.56)	0.26 (0.51)	0.25 (0.36)	.407
Δ $FEF_{25\%}$ (%)	17.34 (34.13)	20.54 (35.70)	20.86 (32.84)	20.18 (34.31)	.433
Δ $FEF_{25\%-75\%}$ (L)	0.39 (0.95)	0.27 (0.57)	0.43 (0.67)	0.61 (0.75)	.105
Δ $FEF_{25\%-75\%}$ (%)	10.37 (22.76)	9.78 (15.85)	15.81 (22.77)	18.45 (25.16)	.180
Δ PEF (L/min)	36.00 (13.20)	64.80 (11.80)	38.80 (15.00)	41.40 (14.10)	.252
Δ PEF (%)	8.44 (19.34)	13.29 (13.24)	11.31 (22.46)	9.00 (17.60)	.346
Δ TLC (L)	0.04 (0.53)	0.04 (0.61)	0.05 (0.56)	−0.05 (0.50)	.864
Δ TLC (%)	1.10 (9.20)	−0.24 (9.40)	1.25 (9.39)	−0.18 (9.66)	.763
Δ RV (L)	0.06 (0.59)	−0.17 (0.66)	−0.13 (0.68)	0.00 (0.46)	.092
Δ RV (%)	5.05 (30.62)	−9.07 (30.00)	−7.61 (34.73)	−2.53 (27.48)	.185
Δ RV/TLC	1.15 (6.86)	−1.90 (10.45)	−2.12 (7.82)	−2.33 (16.24)	.059
Δ RV/TLC (%)	−3.09 (24.17)	−6.27 (19.50)	−7.97 (22.11)	0.38 (23.41)	.351
Δ Beta angle (°)	10.76 (16.44)	5.37 (15.48)	12.73 (18.10)	11.10 (14.40)	.242
Δ $FEF_{50\%}$/PEF	0.09 (0.15)	0.04 (0.13)	0.11 (0.16)	0.09 (0.12)	.151

The p-values <0.05 (with statistical signficance) are put in bold.
Abbreviations: $FEF_{75\%}$, forced expiratory flow at 75% of FVC; $FEF_{50\%}$, forced expiratory flow at 50% of FVC; $FEF_{25\%}$, forced expiratory flow at 25% of FVC; $FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of FVC; FEV_1, forced expiratory volume in 1 second; FVC, forced vital capacity; IL-4R, interleukin 4 receptor; IL-5, interleukin 5; IL-5R, interleukin 5 receptor; PEF, peak expiratory flow; RV, residual volume; TLC, total lung capacity; T0, baseline; T6, 6 months; T12, 12 months.

increase from baseline to T12 (more evident during the first 6 months), as previously described.[23] No significant differences were found between groups at T6 and T12 for FEV_1 in accordance with the results of another study comparing the effectiveness of mepolizumab vs benralizumab vs dupilumab in SA.[24] However, the changes in predicted values were higher in the anti–IL-5R group compared with the others.

Apart from TLC, RV, and RV/TLC, the other lung function parameters included in the study followed the same pattern as FEV_1. They revealed evident improvement at T6, which remained consistent for 12 months, with no significant difference observed between these 2 time points. In this study, omalizumab significantly increased FVC and FEV_1/FVC at T6 and T12 without any effects on lung hyperinflation, in contrast with data from another real-world study that revealed a decrease in RV and RV/TLC at T6.[25] Furthermore, in this study, FVC increased by 0.39 ± 0.46 L at T12 in the anti–IL-5 group comparable with the mean value of 0.33 [95% CI: 0.22-0.44] L found in the MESILICO cohort,[26] At T12, FVC improvement was greater in this study in the group treated by benralizumab than those previously reported (0.35 L vs 0.10 L).[27] A possible benefit on lung hyperinflation was noted at T6 in the groups receiving anti–IL-5/R antibodies, not found at T12 (Table 3). FVC increased by a mean of 0.32 ± 0.51 L at T6 in the anti–IL-4R group, with no effect on lung hyperinflation, in contrast with findings from another small study reporting a larger improvement in FVC by 0.57 [95% CI: −0.06 to 1.20] L after 3 months of treatment with a decrease in RV and RV/TLC.[28] The analysis of FEV_1/FVC trajectories revealed constant improvement over time for the studied biologics, except mepolizumab. Another study described a decline of this ratio after an initial increase during treatment with omalizumab with global stability over time for mepolizumab and dupilumab.[23] A possible explanation for this decrease of FEV_1/FVC could be the suboptimal controller medication adherence found in 63% of patients with SA receiving biologics for several months with an improvement in their asthma

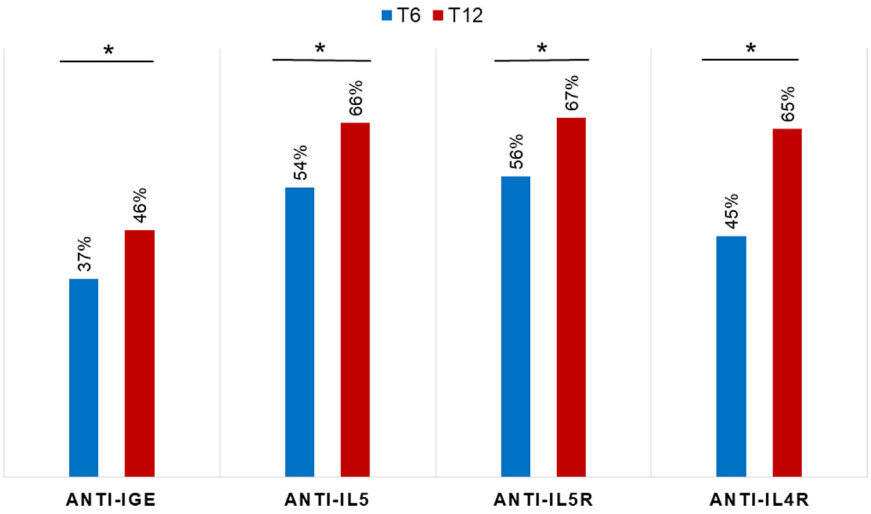

Figure 2. Rate of responses defined as an increase of FEV_1 by more than 10% from baseline for all groups at 6 and 12 months of treatment. Anti-IgE, anti–IgE antibody; anti–IL-5, anti–interleukin 5 antibody; anti–IL-5R, anti–interleukin 5 receptor antibody; anti–IL-4R, anti–interleukin 4 receptor antibody; T6, after 6 months ($P = .012$); T12, after 12 months ($P = .002$). *P value is less than .001.

Table 6
Predictive Factors for the Response to Treatment With Improvement of FEV_1 More Than 10% for the Study Groups

Parameter	Biologic	OR (95% CI)	*P* value
Age	Anti-IgE	0.98 (0.61-1.02)	.226
	Anti–IL-5	1.02 (0.02-1.34)	.225
	Anti–IL-5R	1.03 (0.03-1.51)	.287
	Anti–IL-4R	0.97 (0.03-1.48)	.375
Gender	Anti-IgE	0.55 (0.14-2.13)	.386
	Anti–IL-5	1.15 (0.33-3.95)	.829
	Anti–IL-5R	0.62 (0.14-2.66)	.518
	Anti–IL-4R	0.96 (0.27-3.36)	.949
Smoking	Anti-IgE	0.43 (0.11-1.61)	.205
	Anti–IL-5	0.95 (0.27-3.31)	.938
	Anti–IL-5R	1.29 (0.29-5.66)	.739
	Anti–IL-4R	0.72 (0.20-10.60)	.146
Asthma diagnosis	Anti-IgE	0.40 (0.09-1.78)	.221
	Anti–IL-5	1.94 (0.52-7.17)	.318
	Anti–IL-5R	2.40 (0.64-10.57)	.244
	Anti–IL-4R	2.00 (0.55-7.25)	.289
Atopic dermatitis	Anti-IgE	0.24 (0.03-2.20)	.179
	Anti–IL-5	1.34 (0.20-9.02)	.762
	Anti–IL-5R	0.37 (0.03-4.48)	.419
	Anti–IL-4R	0.56 (0.09-3.49)	.533
Allergic rhinitis	Anti-IgE	0.35 (0.14-0.68)	.183
	Anti–IL-5	0.46 (0.13-1.66)	.233
	Anti–IL-5R	1.93 (0.51-7.31)	.332
	Anti–IL-4R	1.63 (0.39-6.81)	.490
Dysfunctional breathing	Anti-IgE	0.51 (0.09-2.94)	.448
	Anti–IL-5	1.80 (0.15-4.57)	.639
	Anti–IL-5R	-	.257
	Anti–IL-4R	0.43 (0.07-2.51)	.336
GERD	Anti-IgE	1.33 (0.37-4.77)	.658
	Anti–IL-5	0.87 (0.25-3.01)	.829
	Anti–IL-5R	3.67 (0.87-5.38)	.069
	Anti–IL-4R	0.80 (0.23-2.79)	.726
Nasal polyps	Anti-IgE	4.50 (1.16-17.51)	**.026**
	Anti–IL-5	9.00 (1.63-19.76)	**.006**
	Anti–IL-5R	7.00 (1.20-10.83)	**.020**
	Anti–IL-4R	11.11 (0.21-15.76)	**.003**
Obesity	Anti-IgE	0.25 (0.05-1.33)	.089
	Anti–IL-5	0.82 (0.20-3.43)	.790
	Anti–IL-5R	1.62 (0.38-6.94)	.518
	Anti–IL-4R	1.03 (0.25-4.14)	.972
OSA	Anti-IgE	0.39 (0.04-3.89)	.411
	Anti–IL-5	0.25 (0.02-2.68)	.226
	Anti–IL-5R	-	.106
	Anti–IL-4R	0.20 (0.02-1.90)	.130
Psychological disorders	Anti-IgE	0.58 (0.14-2.34)	.443
	Anti–IL-5	1.24 (0.34-4.54)	.474
	Anti–IL-5R	0.75 (0.16-3.62)	.720
	Anti–IL-4R	0.46 (0.12-1.74)	.251

The p-values <0.05 (with statistical signficance) are put in bold.
Abbreviations: FEV_1, forced expiratory volume in 1 second; GERD, gastroesophageal reflux disease; IL-5, interleukin 5; IL-5R, interleukin 5 receptor; IL-4R, interleukin 4 receptor; OR, odds ratio; OSA, obstructive sleep apnea.

outcomes.[29] There are no significant differences between groups for FVC, TLC, and RV at T6 and T12 (except the change in FVC% at T6 in favor of benralizumab) in line with previous data comparing mepolizumab, benralizumab, and dupilumab.[24]

In the context of SAD, a significant feature of SA as found in the ATLANTIS cohort, $FEF_{25\%-75\%}$ and $FEF_{75\%}$ were analyzed. Importantly, the β–angle and $FEF_{50\%}$/PEF, 2 parameters that may indicate distal airway obstruction and are not routinely considered, were measured.[11,15-17] Almost all these parameters were significantly increased after biologics administration (except β–angle and $FEF_{50\%}$/PEF in the anti–IL-5 group at T6), confirming the effectiveness of these treatments in improving SAD. The benefit of omalizumab on SAD was previously demonstrated by real-world studies on the Asiatic population, revealing significant improvement of $FEF_{25\%-75\%}$ (%) after 4 and 12 months of treatment.[30,31] Similar findings were reported in 2 Italian cohorts for mepolizumab after 6 and 12 months of treatment.[32,33] One of them found a significant difference between the mean values of $FEF_{25\%-75\%}$ (%) at T6 and T12, not confirmed by our results.[33] Previous data revealed the positive impact of benralizumab on $FEF_{25\%-75\%}$ (%) after 6 and 12 months of treatment without differences between T6 and T12, as found in this study.[34,35] The improvement of $FEF_{25\%-75\%}$ after treatment by dupilumab in this study is comparable to other data and was described previously, already 4 weeks after biologic initiation.[36,37] Despite the greater mean values of $FEF_{25\%-75\%}$ (%) and $FEF_{75\%}$ (L) registered in this study after treatment in the anti–IL-4R group compared with the others, no significant difference was found between groups for these changes during the study. The trajectories of $FEF_{25\%-75\%}$ and $FEF_{75\%}$ have a comparable ascending pattern for all groups, with a trend of superiority for the anti–IL-4R antibody. The increase over time of both indices, reflecting the upward concavity of the flow-volume curve, is identical, confirming the positive impact of all studied biologics on distal airway obstruction. Benralizumab tends to have a higher impact on distal airway obstruction, even though the results are not significant. These parameters were never analyzed previously in patients with SA treated with biologics, so comparisons with other real-world studies are impossible.

The rate of responders to treatment was significantly higher in patients receiving biologics targeting eosinophilic inflammation than in those treated with anti-IgE antibody. This is an expected result because airway eosinophilic inflammation is the main driver of lung function impairment, frequently associated with an accelerated decline of FEV_1 and more chances of developing irreversible airflow

obstruction.[8,38,39] In this study, the presence of nasal polyps was identified as a predictive factor for response to biologic therapy. Likewise, data from the International Severe Asthma Registry revealed that patients with chronic rhinosinusitis with or without nasal polyps have greater chances of improving their FEV_1 at T6 of biologic therapy.[40]

The originality of this study is the comparison of the impact of 4 different biologics on a large panel of lung function parameters, including SAD, in real-world settings. In addition, for the first time in the literature, 2 indices, β−angle and $FEF_{50\%}$/PEF, which could reflect distal airway obstruction even in patients with a normal FEV_1/FVC were assessed. Several limitations inherent to the observational nature of this research should be considered. These include potential baseline heterogeneity between groups in terms of gender, asthma onset age, and comorbidity profiles, the relatively small number of participants, and the variability in lung function testing equipment used across the 3 centers.

In conclusion, omalizumab, mepolizumab, benralizumab, and dupilumab demonstrate comparable effectiveness in improving lung function parameters, including those related to SAD after 6 and 12 months of treatment in patients with SA. Benralizumab demonstrated a higher benefit than the other treatments for FEV_1 improvement. The biologics targeting eosinophilic inflammation seem to be more effective in improving FEV_1 by more than 10% from baseline compared with the anti-IgE antibody. The presence of nasal polyps increases the chance of a response to biologic therapy. Trends for greater effectiveness of dupilumab in improving SAD and benralizumab on distal airway obstruction were noted, even though the results did not always reach significance. These findings should be confirmed by future larger studies.

Disclosures

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