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Original Research

Real-world comparison of T2-biologics effectiveness in severe allergic asthma with nasal polyps

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ABSTRACT

Background: Patients with severe allergic asthma (SAA) and blood eosinophil count $\geq 0.3x10^9$/L are eligible for multiple biologics. Several of them showed benefits on nasal polyps (NP), a frequent comorbidity of the severe asthma, but comparative studies on their effectiveness in the association SAA-NP are currently lacking.
Our objective: was to compare the effectiveness of anti-IgE, anti-IL5/R and anti-IL4R in patients with SAA-NP in real-world settings.
Methods: A real-world multicentre observational study was realized including patients with SAA-NP treated by anti-IgE, anti-IL5/R or anti-IL4R for 6 months. We analyzed the nasal and respiratory symptoms, the number of asthma attacks and salbutamol use/week, acute sinusitis and severe exacerbation rates, the asthma control score, the lung function parameters, the NP endoscopic score, the sinus imaging, and the blood eosinophil count 6 months before and after treatment.
Results: One hundred seven patients with SAA-NP were included: 35 treated by anti-IgE, 38 by anti-IL5/R and 34 by anti-IL4R. All the biologics showed similar effectiveness in improving asthma outcomes (symptoms, exacerbation rate, asthma control, lung function). Despite the amelioration of almost all rhinological parameters and sinus imaging in each group, greater benefits were found in the anti-IL4R group in terms of loss of smell (odds ratio OR 3.64[1.3–11.1], p = 0.017), nasal obstruction (OR12.00[2.00–23.10], p = 0.023), and NP endoscopic score (OR 18.10[4.43–24.50]).
Conclusion: All three biological classes improved asthma and sino-nasal outcomes in patients with SAA-NP. However, anti-IL4R was superior in improving the smell, nasal obstruction, and NP endoscopic size. Larger comparative studies are needed to confirm our results.

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Abbreviations

ICS	inhaled corticosteroids
LABA	long-acting β2 receptors agonists
SAA	severe allergic asthma
IgE	immunoglobulin E
BEC	blood eosinophil count
Anti-IgE:	anti-immunoglobulin E antibody
Anti-IL-5/R	anti-interleukin 5 and anti-interleukin 5 receptor antibodies
Anti-IL-4R	anti-interleukin 4 receptor antibody
NP	nasal polyps
IL-4	interleukin 4
IL-5	interleukin 5
IL-13	interleukin 13
ENT	Ear Nose Throat
T0	at baseline
T6	after 6 months of treatment
SABA	short-acting β2 receptors agonists
ACT	Asthma Control Test
FEV1	forced expiratory volume in 1 s
FVC	forced vital capacity
SCS	systemic corticosteroids
LoS	loss of smell score
VAS	visual analogue scale of symptoms
CRS	chronic rhinosinusitis
CT	computed tomography
LMS	Lund-Mackay staging
SD	standard deviation
OR	odds ratios
R-hat	potential scale reduction factor
ESS	effective sample size
RCTs	randomized controlled trials

1. Introduction

Severe asthma is defined as an uncontrolled disease despite adherence with maximal optimized treatment by high-dose inhaled corticosteroids associated to long-acting beta agonists (ICS-LABA) and management of contributory factors or requiring this treatment to maintain good symptom control and reduce the risk of exacerbations. Despite low prevalence (~4 % of asthmatics), the social-economic burden of severe asthma is significant due to increased healthcare costs, high rate of absenteeism, and poor patients' quality of life [1]. Severe asthma is a heterogenous syndrome encompassing different clinical and biological phenotypes [2]. About 70 % of patients have severe allergic asthma (SAA), a phenotype characterized by the presence of clinically apparent allergic reaction and an immunoglobulin E (IgE) response to specific aeroallergens [3–6]. In the other hand, the eosinophilic inflammation is found in up to 60 % of severe asthma patients when the cut-off is a blood eosinophils count (BEC) $\geq 0.3x10^9$/L and exceeds 80 % if the cut-off is $\geq 0.15x10^9$/L [5,7]. As the eosinophil is a hallmark of allergy, about 35 % of patients with severe asthma have overlapping phenotypes (eosinophilia and allergy), so they are eligible for multiple biological classes targeting IgE, interleukin 5 (IL5) or its receptor (IL5R) on eosinophils and interleukin 4 receptor (IL4R), making the choice difficult in clinical practice [1,2,5,8].

Nasal polyps (NP) represent a common comorbidity of severe asthma with a prevalence of 36 % compared to only 4 % in the general population [5,6,9,10]. This prevalence increases up to 71 % in patients with severe eosinophilic asthma and allergic background [5]. Although not life-threatening, NP have a negative socio-economic impact leading to loss of productivity and increased healthcare use, but also the consequences on associated asthma (poor symptom control, high risk of exacerbations, altered lung function) [9–11]. Usually, NP exhibits type 2-inflammation with secretion of IL4, IL5, IL13 and IgE, so most biologics developed for severe asthma targeting these molecules showed benefits on NP outcomes [1,9,12]. The possibility to treat by a single agent asthma and NP is an exciting prospect in the era of personalized medicine. However, head-to-head comparisons on the effectiveness of biologics in the association SAA-NP are limited.

The aim of this study was to compare the effectiveness of anti-IgE, anti-IL5/R, and anti-IL4R antibodies in patients with SAA and NP in real-world settings. We previously published a comparative study of anti-IgE, anti-IL5 and anti-IL5R effectiveness in patients with SAA-NP, but with the arrival of the anti-IL4R that could be prescribed as add-on therapy in severe asthma and NP, we consider that a new analysis including this therapeutic class could be interesting for the clinicians [13].

2. Methods

2.1. Study design and participants

An observational, multicentre, real-world study was performed using data from medical records of patients with the association SAA-NP in the Departments of Pulmonology of the Hospitals of Besançon, Colmar, Dijon, Nancy, Strasbourg (France) and Santiago de Compostela (Spain) from December 1, 2016 to December 31, 2022. The study was approved by the Institutional Review Board of the French learned society for respiratory medicine – Société de Pneumologie de Langue Française (CEPRO 2022-032) and the Santiago and Lugo Research and Ethics Committee (number 2019/438). All patients provided written informed consent before extracting and using their data.

Inclusion criteria were adult SAA patients meeting criteria to receive a biologic and naive for such treatment, with associated NP diagnosed by an Ear Nose Throat (ENT) specialist already treated by daily nasal corticosteroids without local antihistamines [1,3,10,14]. Each respiratory physician chose the biologics for its patients according to the individual clinical and biological criteria, but also the availability of these treatments in his country. All the respiratory physicians involved in the study are also allergy specialists. A duration of minimum 6 months of treatment was mandatory for the inclusion. Patients who refused collection of their medical data, those receiving daily oral corticosteroids and/or with incomplete information according to the study parameters were excluded.

Skin prick tests to common aeroallergens were performed for all patients to confirm the atopy [15]. The sensitization to at least one perennial allergen was documented before starting a treatment by anti-IgE antibody. Once daily systemic antihistamines were administered in all patients for their symptoms related to allergic rhinitis.

According to the chosen biologic, the patients were distributed in three different groups: group 1 treated by anti-IgE (omalizumab), group 2 by anti-IL5/R (mepolizumab or benralizumab), and group 3 by anti-IL4R (dupilumab). Data from electronic patient files were recorded at the initiation of biologic (T0) and at 6 months (T6) to evaluate the response to treatment. Data extraction was done progressively with the inclusions in the study from December 1, 2019 to December 31, 2022.

2.2. Outcomes

Asthma evaluation included clinical variables (dyspnoea, cough, number of daytime and nocturnal attacks/week, number of short-acting β2 receptors agonists [SABA] use/week, Asthma Control Test [ACT] score, number of severe exacerbations/6 months), and lung function

parameters (forced expiratory volume in 1 s- FEV1; forced vital capacity-FVC and FEV1/FVC ratio) measured according to standardized methods, at T0 and T6 [16]. ACT scores ≥20 corresponds to well-controlled asthma while ACT<20 to poorly controlled asthma and change of ≥3 points was considered as clinically important in an individual patient [17]. Severe exacerbation was defined as worsening of symptoms for ≥3 days requiring systemic corticosteroids (SCS) and/or hospitalisation.

The ENT assessment comprised symptoms, loss of smell (LoS) score, visual analogue scale (VAS) for chronic rhinosinusitis (CRS), number of acute sinusitis episodes/6 months, endoscopic NP score and sinus computed tomographic (CT) images, at T0 and T6. LoS score grades from 0-no symptom to 3-severe symptom. VAS score >5 cm "present/impaired" symptoms while VAS≤5 cm, "not bothersome" [14]. Acute sinusitis was defined as the presence of nasal obstruction, purulent secretion in cavum nasi, local pain and fever (>38 °C) for ≥5 days requiring antibiotics ± corticosteroids. The endoscopic score graded NP based on their size for each nostril separately (0-no polyps; 1-small polyps in the middle meatus not reaching below the inferior border of middle turbinate, 2-polyps reaching below the lower border of the middle turbinate; 3-large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle turbinate; 4-large polyps causing complete obstruction of the inferior nasal cavity) and added, resulting in a value between 0 and 8 [10]. The Lund-Mackay staging (LMS) was used to estimate the severity of CRS on sinus CT-scan with scores ranging from 0 to 24 [18].

As biomarker of T2-inflammation, the BEC was measured at T0 and T6.

2.3. Statistical analysis

Statistical analysis was performed using the SPPS program version (SAS Institute, Cary, NC, USA) and R software (version 4.2.2; R Foundation, Vienna, Austria). Quantitative variables were expressed as mean values ± standard deviation (SD), and qualitative variables as number (percentage). Comparisons among the three groups were performed using an ANOVA test and Tukey-Kramer procedure if the distribution was normal, or Kruskal–Wallis test, if the distribution was not normal. Comparisons of values between two groups and T0 vs T6 were performed using Fisher's test for qualitative variables and T-test for quantitative variables.

For the assessment of response to biologics, the differences between T6 and T0 (Δ = values at 6 months minus baseline values) of studied parameters were compared by using Anova method and the relative risk of success at T6 by binary logistic regression. The odds ratios (OR) were calculated with anti-IgE as reference group compared to anti-IL5/R and anti-IL4R groups. For VAS and NP scores, Bayesian univariate logistic regression method was performed (using Rstanarm package) as frequentist logistic regression was not possible because some groups exhibited 100 % success rate. Non informative prior for the regression coefficient was given by a Normal distribution N (0,0.428) hypothesizing an OR distribution between about 0.05 and 20. The convergence of the model was checked using trace plots and examining the potential scale reduction factor (R-hat) and the resolution of the chains was assessed by the measure of the effective sample size (ESS). Multivariate logistic regression was performed to assess the association between the reduction of exacerbation rate with the use of each biologic. Adjustments were performed for exacerbation rate, blood eosinophil count and FEV1 at baseline. The posterior distributions were described numerically by their mean OR and (2.5 %, 97.5 %) intervals. The limit of significance was $p < 0.05$.

Following criteria were used to evaluate the response to biologics at T6: any change in the respiratory and ENT symptoms from "severe" to "inexistent" or "normal" between T0 and T6, decrease of asthma exacerbation and sinusitis rates ≥50 % per 6 months, LoS score increase by ≥ 0.5, no night and ≤2 diurnal attacks/week, ACT score ≥20, increase of ACT score by ≥ 3 points, VAS total ENT symptoms reduction of ≥2 cm, SABA use ≤2/week, NP endoscopic score decrease by ≥ 1, a change >10 % of FEV1 or FVC, LMS improvement by ≥ 5 and a BEC $<0.15x10^9$/L at T6. These criteria of response were selected from current guidelines and data from the literature [17,19–22].

3. Results

3.1. Baseline characteristics (T0)

One hundred seven patients with SAA-NP eligible for biologics as add-on treatment for their asthma were included and divided into three groups according to the chosen therapy (Table 1). Sixty-four patients (59.8 %) were included in the University Hospital of Nancy (as the promoter center of the study), 11 patients (10.3 %) in the University Hospital of Strasbourg, 10 patients (9.3 %) in the University Hospital of Santiago de Compostela, 8 patients (7.5 %) in the University Hospital of Besançon, with an equal contribution of 7 patients (6.5 %) in the University Hospital of Dijon and Hospital of Colmar. The mean age of the study population was 52 ± 13 years. There was a predominance of males, never-smokers, and adult-onset of asthma. A high proportion of patients had previous NP surgery (68.2 %). All patients were allergic with increased IgE serum levels without differences between groups concerning the presence of aspirin intolerance. The distribution of the sensitization to aeroallergens was homogenous between the groups except for pollens, more frequent in the anti-IL4R group. In the group anti-IgE, the prevalence of familial asthma and atopy were increased

Table 1
Descriptive parameters of the study population at baseline according to treatment group.

Parameter	All patients (N = 107)	Group 1 Anti-IgE (N = 35)	Group 2 Anti-IL5/R (N = 38)	Group 3 Anti-IL4R (N = 34)	p-value
Age, mean (SD)	52.1 (12.7)	50.8 (14.9)	54.4 (10.9)	50.9 (12.0)	0.339
Male, *n* (%)	63 (58.9 %)	22 (62.9 %)	21 (55.3 %)	20 (58.8 %)	0.805
Adult-onset asthma, *n* (%)	79 (73.8 %)	29 (82.9 %)	30 (78.9 %)	20 (58.8 %)	0.051
Family history, *n* (%)					
Asthma	33 (30.8 %)	16 (45.7 %)	4 (10.5 %)	13 (38.2 %)	**0.024**
Atopy	39 (36.4 %)	20 (57.1 %)	5 (13.2 %)	14 (41.2 %)	**0.007**
Previous NP surgery, *n* (%)	73 (68.2 %)	24 (68.6 %)	23 (60.5 %)	26 (76.5 %)	0.349
Smoking history, *n* (%)					
Never-smoker	74 (69.2 %)	22 (62.9 %)	29 (76.3 %)	23 (67.7 %)	
Ex-smoker	33 (30.8 %)	12 (34.3 %)	9 (23.7 %)	12 (32.3 %)	0.503
Active smoker	1 (0.9 %)	1 (2.9 %)	0 (0.0 %)	0 (0.0 %)	
Pack-years, mean (SD)	3.5 (6.7)	4.9 (8.6)	2.4 (4.9)	3.4 (5.9)	0.406
Sensitizations, *n* (%)					
House dust mite	74 (69.2 %)	27 (77.1 %)	24 (63.2 %)	23 (67.6 %)	0.413
Pets	46 (43.4 %)	13 (37.1 %)	13 (34.2 %)	20 (60.6 %)	0.054
Molds	28 (26.4 %)	9 (25.7 %)	13 (34.2 %)	6 (18.2 %)	0.309
Pollens	54 (50.9 %)	14 (40.0 %)	16 (42.1 %)	24 (72.7 %)	**0.010**
Aspirin intolerance, *n* (%)	21 (19.6 %)	10 (28.6 %)	5 (13.2 %)	6 (17.7 %)	0.238
Total serum IgE, mean (SD) (UI/mL)	498.1 (614.1)	537.3 (442.6)	477.6 (481.4)	480.8 (864.6)	0.392

IgE: immunoglobulin E; IL5/R: interleukin 5 and interleukin 5 receptor; IL4R: inteleukin 4 receptor; NP: nasal polyps.

compared to the others.

The most common ENT symptoms were nasal obstruction (less frequent in the group anti-IgE), loss of smell, and rhinorrhea. The VAS score was significantly lower in the anti-IgE group compared to the others (Table 2). At baseline, the groups were comparable in terms of the respiratory symptoms, asthma attacks and SABA use per week. The ACT score was higher in the anti-IgE group vs anti-IL5/R group (12.0 ± 3.8 vs 10.0 ± 3.8, p = 0.039). The rates of acute sinusitis and asthma exacerbations per 6 months were lower in the anti-IL4R group compared to the anti-IgE group. No difference was found for the lung function parameters between the groups. The anti-IL4R group has lower BEC and LMS, but higher endoscopic NP score compared to the others (Table 2). The only significant difference between the anti-IL5 and anti-IL5R groups was for the VAS score (6.5 ± 1.8 vs 7.8 ± 0.8, p = 0.003) (Table 3).

3.2. Outcome measures (T6)

Almost all the study parameters were significantly improved after 6 months of treatment except the pruritus and FEV1/FVC in the anti-IL5/R group, the NP endoscopic score and FEV1/FVC in the anti-IgE group, the FVC and BEC in the anti-IL4R group (Table 4, Figs. 1 and 2).

At T6, the benefits on the respiratory symptoms, asthma attacks, ACT score, and SABA use per week were comparable for all groups (Table 2). The only one change reaching significance was for the ACT score, with a better improvement in the anti-IL5/R group compared to the others (Table 5). Despite lower exacerbation rates in the anti-IL5/R and anti-IL4R groups than in the anti-IgE group, the changes were similar. Concerning the lung function parameters, the effectiveness of biologics was comparable for the three groups, but the FEV1/FVC was higher in the group anti-IL4R (72.7 ± 10.6) compared to the anti-IL5/R (67.7 ± 9.9) and anti-IgE groups (67.2 ± 10.0) (p = 0.047) (Tables 2 and 5).

Table 2
Comparison of study parameters between groups at baseline (T0) and after 6 months (T6) of treatment.

Parameter	Group 1 Anti-IgE (N = 35)	Group 2 Anti-IL5/R (N = 38)	Group 3 Anti-IL4R (N = 34)	1 vs 2 p-value	2 vs 3 p-value	1 vs 3 p-value	p-value
At baseline (T0)							
ENT symptoms, *n* (%)							
Pruritus	19 (54.3)	20 (52.6)	18 (52.9)	0.887	0.872	0.983	0.974
Loss of smell	33 (94.3)	35 (92.1)	30 (88.2)	0.713	0.551	0.352	0.415
Rhinorrhea	34 (97.1)	34 (89.5)	33 (97.0)	0.195	0.218	0.966	0.446
Sneeze	22 (62.9)	23 (60.5)	22 (64.7)	0.838	0.788	0.947	0.909
Nasal obstruction	30 (85.7)	37 (97.4)	34 (100)	0.070	0.348	**0.024**	**0.044**
LoS score, mean (SD)	1.3 (0.6)	1.3 (0.6)	1.4 (0.7)	0.996	0.530	0.532	0.805
VAS score, mean (SD)	6.0 (1.5)	7.1 (1.6)	7.0 (1.0)	**0.003**	0.675	**0.003**	**0.027**
Respiratory symptoms							
Dyspnoea, mean MMRC (SD)	2.2 (0.9)	2.2 (0.9)	1.9 (1.0)	0.941	0.239	0.270	0.338
Cough, *n* (%)	30 (85.7)	35 (92.1)	28 (82.4)	0.383	0.194	0.663	0.457
Daily attacks/week, mean (SD)	5.9 (2.9)	5.6 (3.1)	4.6 (2.7)	0.621	0.071	0.054	0.058
Nocturnal attacks/week, mean (SD)	3.2 (2.0)	3.3 (2.0)	3.4 (2.6)	0.761	0.941	0.746	0.886
ACT score, mean (SD)	12.0 (3.8)	10.0 (3.8)	11.4 (3.6)	**0.039**	0.117	0.381	0.064
Acute sinusitis/6 months, mean (SD)	3.3 (2.1)	2.7 (1.4)	2.3 (1.5)	0.103	0.227	**0.022**	**0.045**
Exacerbations/6 months, mean (SD)	4.0 (1.4)	3.7 (1.7)	3.3 (1.4)	0.201	0.290	**0.026**	0.067
SABA use/week, mean (SD)	14.4 (7.3)	15.0 (9.0)	15.7 (8.9)	0.745	0.737	0.676	0.910
Lung function, mean (SD)							
FEV1 (% predicted)	64.5 (17.4)	69.4 (23.1)	72.4 (17.3)	0.294	0.536	0.065	0.178
FVC (% predicted)	85.1 (15.7)	89.7 (22.8)	91.9 (15.9)	0.137	0.632	0.075	0.071
FEV1/FVC (%)	63.4 (13.2)	63.2 (12.6)	66.5 (12.2)	0.873	0.259	0.320	0.459
LMS, mean (SD)	12.0 (1.4)	12.0 (1.1)	10.9 (1.3)	0.993	**<0.001**	**0.003**	**0.002**
NP endoscopic score, mean (SD)	3.8 (1.5)	4.9 (1.2)	5.6 (1.4)	**0.001**	**0.047**	**<0.001**	**<0.001**
BEC ($\times 10^9$/L), mean (SD)	0.8 (0.5)	0.8 (0.4)	0.6 (0.4)	0.993	**0.022**	**0.038**	**0.013**
After 6 months (T6)							
ENT symptoms, *n* (%)							
Pruritus	1 (2.9)	16 (42.1)	4 (11.8)	**<0.001**	**0.003**	0.158	**<0.001**
Loss of smell	21 (60.0)	24 (63.2)	10 (29.4)	0.782	**<0.001**	**0.002**	**0.009**
Rhinorrhea	24 (68.6)	19 (50.0)	12 (35.3)	0.107	**0.027**	**<0.001**	**0.010**
Sneeze	4 (11.4)	12 (31.6)	8 (23.5)	**0.038**	0.454	0.190	0.117
Nasal obstruction	18 (51.4)	16 (42.1)	4 (11.8)	0.425	**<0.001**	**<0.001**	**<0.001**
LoS score, mean (SD)	0.8 (0.7)	0.9 (0.8)	0.3 (0.5)	0.585	**<0.001**	**0.002**	**0.009**
VAS score, mean (SD)	2.5 (2.1)	3.1 (2.4)	1.2 (1.0)	0.261	**<0.001**	**0.001**	**0.002**
Respiratory symptoms							
Dyspnoea, mean MMRC (SD)	0.9 (0.8)	1.0 (1.0)	0.8 (0.9)	0.687	0.254	0.561	0.537
Cough, *n* (%)	16 (45.7)	14 (36.8)	9 (26.5)	0.441	0.353	0.099	0.251
Daily attacks/week, mean (SD)	1.3 (1.4)	1.0 (2.1)	0.8 (1.8)	0.494	0.660	0.203	0.457
Nocturnal attacks/week, mean (SD)	0.5 (0.9)	0.3 (0.9)	0.2 (1.2)	0.283	0.656	0.194	0.227
ACT score, mean (SD)	19.8 (3.4)	20.6 (4.5)	20.1 (4.9)	0.116	0.658	0.797	0.311
Acute sinusitis/6 months, mean (SD)	1.0 (1.4)	0.3 (0.6)	0.2 (0.4)	**0.005**	0.358	**0.001**	**0.003**
Exacerbations/6 months, mean (SD)	1.1 (1.4)	0.6 (1.0)	0.3 (0.6)	**0.044**	0.143	**0.001**	**0.005**
SABA use/week, mean (SD)	2.9 (3.1)	3.0 (6.7)	2.3 (4.1)	0.944	0.597	0.482	0.676
Lung function							
FEV1 (% predicted)	78.1 (18.8)	84.3 (21.2)	85.7 (19.7)	0.187	0.788	0.107	0.227
FVC (% predicted)	97.3 (21.8)	103.7 (23.5)	99.3 (15.2)	0.229	0.354	0.655	0.454
FEV1/FVC (%)	67.2 (10.0)	67.7 (9.9)	72.7 (10.6)	0.826	**0.043**	**0.030**	**0.047**
LMS,mean (SD)	9.2 (2.6)	8.5 (2.5)	6.7 (2.4)	0.298	**0.005**	**<0.001**	**<0.001**
NP endoscopic score, mean (SD)	3.1 (1.3)	2.7 (1.8)	1.4 (1.0)	0.263	**<0.001**	**<0.001**	**<0.001**
BEC ($\times 10^9$/L), mean (SD)	0.5 (0.3)	0.1 (0.2)	0.7 (0.7)	**<0.001**	**<0.001**	0.137	**<0.001**

IgE: immunoglobulin E; IL5/R: interleukin 5/5 receptor; IL4R: inteleukin 4 receptor; ENT: ear-nose-throat; LoS: loss of smell; SD: standard deviation; VAS: visual analog scale; MMRC: modified Medical Research Council scale; ACT: Asthma Control Test; SABA: Short-Acting Beta-Agonists; FEV1: Forced Expiratory Volume at the end of the first second; FVC: Forced Vital Capacity; LMS: Lund-Mackay staging; NP: nasal polyps BEC: blood eosinophil count.

Table 3
Comparison of study parameters between anti-IL5R subgroup vs anti-IL5 subgroup at baseline (T0) and after 6 months of treatment (T6).

Parameter	Subgroup Anti-IL5 (N = 21)	Subgroup Anti-IL5R (N = 17)	p-value
At baseline			
ENT symptoms, n (%)			
Pruritus	9 (43)	11 (65)	0.198
Loss of smell	18 (86)	17 (100)	0.230
Rhinorrhea	17 (81)	17 (100)	0.144
Sneeze	10 (48)	13 (76)	0.136
Nasal obstruction	20 (95)	17 (100)	0.197
LoS score, mean (SD)	1.2 (0.7)	1.5 (0.5)	0.098
VAS score, mean (SD)	6.5 (1.8)	7.8 (0.8)	**0.003**
Respiratory symptoms			
Dyspnoea, mean MMRC (SD)	2.1 (0.9)	2.3 (0.8)	0.518
Cough, n (%)	20 (95)	15 (88)	0.577
Daily attacks/week, mean (SD)	5.2 (3.1)	6.0 (3.0)	0.405
Nocturnal attacks/week, mean (SD)	3.2 (2.0)	3.5 (1.8)	0.559
Acute sinusitis/6 months, mean (SD)	2.6 (1.6)	2.8 (1.2)	0.447
Exacerbations/6 months, mean (SD)	4.0 (1.9)	3.2 (1.4)	0.252
SABA use/week, mean (SD)	15.7 (10.3)	14.2 (7.4)	0.871
ACT score, mean (SD)	10.7 (3.6)	9.7 (3.1)	0.400
Lung function			
FEV1 (% predicted)	69.6 (24.6)	69.1 (21.7)	0.826
FVC (% predicted)	87.1 (24.8)	92.8 (20.3)	0.780
FEV1/FVC (%)	64.7 (10.9)	61.3 (13.9)	0.528
LMS, mean (SD)	12.1 (1.2)	11.9 (1.1)	0.744
NP endoscopic score, mean (SD)	4.7 (1.4)	5.2 (1.0)	0.402
BEC ($x10^9$/L), mean (SD)	0.9 (0.4)	0.7 (0.4)	0.246
After 6 months			
ENT symptoms, n (%)			
Pruritus	9 (43)	7 (41)	0.733
Loss of smell	12 (57)	12 (71)	0.710
Rhinorrhea	10 (48)	9 (53)	0.389
Sneeze	7 (33)	5 (29)	0.796
Nasal obstruction	10 (48)	6 (35)	0.749
LoS score, mean (SD)	0.8 (0.8)	0.9 (0.7)	0.610
VAS score, mean (SD)	3.0 (2.5)	3.1 (2.3)	0.870
Respiratory symptoms			
Dyspnoea, mean MMRC (SD)	1.0 (1.1)	1.1 (0.9)	0.421
Cough, n (%)	10 (48)	4 (24)	0.126
Daily attacks/week, mean (SD)	1.5 (2.4)	0.5 (1.5)	0.142
Nocturnal attacks/week, mean (SD)	0.5 (1.1)	0.1 (0.5)	0.240
Acute sinusitis/6 months, mean (SD)	0.4 (0.7)	0.1 (0.3)	0.121
Exacerbations/6 months, mean (SD)	0.9 (1.2)	0.2 (0.4)	**0.020**
SABA use/week, mean (SD)	4.6 (8.4)	0.9 (2.9)	0.095
ACT score, mean (SD)	19.7 (4.8)	21.6 (4.0)	0.213
Lung function			
FEV1 (% predicted)	80.3 (20.8)	89.4 (21.1)	0.177
FVC (% predicted)	98.8 (22.7)	109.8 (23.7)	**0.043**
FEV1/FVC (%)	67.8 (8.4)	67.5 (11.7)	0.670
LMS, mean (SD)	9.5 (2.0)	7.5 (2.6)	**0.006**
NP endoscopic score, mean (SD)	2.8 (2.1)	2.6 (1.5)	0.785
BEC ($x10^9$/L), mean (SD)	0.2 (0.2)	0.0 (0.0)	**<0.001**

IL5: interleukin 5; IL5R: interleukin 5 receptor; ENT: ear-nose-throat; LoS: loss of smell; SD: standard deviation; VAS: visual analog scale; MMRC: modified Medical Research Council scale; SABA: Short-Acting Beta-Agonists; ACT: Asthma Control Test; FEV1: Forced Expiratory Volume at the end of the first second; FVC: Forced Vital Capacity; LMS: Lund-Mackay staging; NP: nasal polyps BEC: blood eosinophil count.

Table 4
Comparative analysis of study parameters at baseline (T0) and 6 months of treatment (T6) for each group.

Group	Parameter	At baseline	At 6 months	p-value
Group 1	**ENT symptoms,** n (%)			
Anti-IgE	Pruritus	19 (54.3)	1 (2.9)	**<0.001**
(N = 35)	Loss of smell	33 (94.3)	21 (60.0)	**<0.001**
	Rhinorrhea	34 (97.1)	24 (68.6)	**<0.001**
	Sneeze	22 (64.7)	4 (11.4)	**<0.001**
	Nasal obstruction	30 (85.7)	18 (51.4)	**<0.001**
	LoS score, mean (SD)	1.3 (0.6)	0.8 (0.7)	**<0.001**
	VAS score, mean (SD)	6.0 (1.5)	2.5 (2.1)	**<0.001**
	Respiratory symptoms			
	Dyspnoea, mean MMRC (SD)	2.2 (0.9)	0.9 (0.8)	**<0.001**
	Cough, n (%)	30 (85.7)	16 (45.7)	**0.001**
	Daily attacks/week, mean (SD)	5.9 (2.9)	1.3 (1.4)	**<0.001**
	Nocturnal attacks/ week, mean (SD)	3.2 (2.0)	0.5 (0.9)	**<0.001**
	ACT score, mean (SD)	12.0 (3.8)	19.8 (3.4)	**<0.001**
	Acute sinusitis/6 months, mean (SD)	3.3 (2.1)	1.0 (1.4)	**<0.001**
	Exacerbations/6 months, mean (SD)	4.0 (1.4)	1.1 (1.4)	**<0.001**
	SABA use/week, mean (SD)	14.4 (7.3)	2.9 (3.1)	**<0.001**
	Lung function			
	FEV1 (% predicted)	64.5 (17.4)	78.1 (18.8)	**0.003**
	FVC (% predicted)	85.1 (15.7)	97.3 (21.8)	**0.009**
	FEV1/FVC (%)	63.4 (13.2)	67.2 (10.0)	0.183
	LMS, mean (SD)	12.0 (1.4)	9.2 (2.6)	**<0.001**
	NP endoscopic score, mean (SD)	3.8 (1.5)	3.1 (1.3)	0.055
	BEC ($\times 10^9$/L), mean (SD)	0.8 (0.5)	0.5 (0.3)	**0.001**
Group 2	**ENT symptoms,** n (%)			
Anti-IL5/	Pruritus	20 (52.6)	16 (42.1)	0.324
R (N = 38)	Loss of smell	35 (92.1)	24 (63.2)	**0.005**
	Rhinorrhea	34 (89.5)	19 (50.0)	**<0.001**
	Sneeze	23 (60.5)	12 (31.6)	**0.006**
	Nasal obstruction	37 (97.4)	16 (42.1)	**<0.001**
	LoS score, mean (SD)	1.3 (0.6)	0.9 (0.8)	**0.005**
	VAS score, mean (SD)	7.1 (1.6)	3.1 (2.4)	**<0.001**
	Respiratory symptoms			
	Dyspnoea, mean MMRC (SD)	2.2 (0.9)	1.0 (1.0)	**<0.001**
	Cough, n (%)	35 (92.1)	14 (36.8)	**<0.001**
	Daily attacks/week, mean (SD)	5.6 (3.1)	1.0 (2.1)	**<0.001**
	Nocturnal attacks/ week, mean (SD)	3.3 (2.0)	0.3 (0.9)	**<0.001**
	ACT score, mean (SD)	10.0 (3.8)	20.6 (4.5)	**<0.001**
	Acute sinusitis/6 months, mean (SD)	2.7 (1.4)	0.3 (0.6)	**<0.001**
	Exacerbations/6 months, mean (SD)	3.7 (1.7)	0.6 (1.0)	**<0.001**
	SABA use/week, mean (SD)	15.0 (9.0)	3.0 (6.7)	**<0.001**
	Lung function			
	FEV1 (% predicted)	69.4 (23.1)	84.3 (21.2)	**0.004**
	FVC (% predicted)	89.7 (22.8)	103.7 (23.5)	**0.010**
	FEV1/FVC (%)	63.2 (12.6)	67.7 (9.9)	0.082
	LMS, mean (SD)	12.0 (1.1)	8.5 (2.5)	**<0.001**
	NP endoscopic score, mean (SD)	4.9 (1.2)	2.7 (1.8)	**<0.001**
	BEC ($\times 10^9$/L), mean (SD)	0.8 (0.4)	0.1 (0.2)	**<0.001**
Group 3	**ENT symptoms,** n (%)			
Anti-IL4R	Pruritus	18 (52.9)	4 (11.8)	**<0.001**
(N = 34)	Loss of smell	30 (88.2)	10 (29.4)	**<0.001**
	Rhinorrhea	33 (97.0)	12 (35.3)	**<0.001**
	Sneeze	22 (64.7)	8 (23.5)	**<0.001**
	Nasal obstruction	34 (100)	4 (11.8)	**<0.001**
	LoS score, mean (SD)	1.4 (0.7)	0.3 (0.5)	**<0.001**
	VAS score, mean (SD)	7.0 (1.0)	1.2 (1.0)	**<0.001**
	Respiratory symptoms			

(*continued on next page*)

Table 4 (*continued*)

Group	Parameter	At baseline	At 6 months	p-value
	Dyspnoea, mean MMRC (SD)	1.9 (1.0)	0.8 (0.9)	**<0.001**
	Cough, n (%)	28 (82.4)	9 (26.5)	**<0.001**
	Daily attacks/week, mean (SD)	4.6 (2.7)	0.8 (1.8)	**<0.001**
	Nocturnal attacks/ week, mean (SD)	3.4 (2.6)	0.2 (1.2)	**<0.001**
	ACT score, mean (SD)	11.4 (3.6)	20.1 (4.9)	**<0.001**
	Acute sinusitis/6 months, mean (SD)	2.3 (1.5)	0.2 (0.4)	**<0.001**
	Exacerbations/6 months, mean (SD)	3.3 (1.4)	0.3 (0.6)	**<0.001**
	SABA use/week, mean (SD)	15.7 (8.9)	2.3 (4.1)	**<0.001**
	Lung function			
	FEV1 (% predicted)	72.4 (17.3)	85.7 (19.7)	**0.004**
	FVC (% predicted)	91.9 (15.9)	99.3 (15.2)	0.055
	FEV1/FVC (%)	66.5 (12.2)	72.7 (10.6)	**0.029**
	LMS, mean (SD)	10.9 (1.3)	6.7 (2.4)	**<0.001**
	NP endoscopic score, mean (SD)	5.6 (1.4)	1.4 (1.0)	**<0.001**
	BEC ($\times 10^9$/L), mean (SD)	0.6 (0.4)	0.7 (0.7)	0.494

IgE: immunoglobulin E; IL5/R: interleukin 5/5 receptor; IL4R: inteleukin 4 receptor; ENT: ear-nose-throat; LoS: loss of smell; SD: standard deviation; VAS: visual analog scale; MMRC: modified Medical Research Council scale; ACT: Asthma Control Test; SABA: Short-Acting Beta-Agonists; FEV1: Forced Expiratory Volume at the end of the first second; FVC: Forced Vital Capacity; LMS: Lund-Mackay staging; NP: nasal polyps BEC: blood eosinophil count.

For the ENT symptoms, a greater benefit was found on sneeze and nasal pruritus in the anti-IgE group compared to the others, while the anti-IL4R was more effective to improve the smell, rhinorrhea, nasal obstruction, and the VAS score (Tables 2 and 5). Similar effects were found in decreasing the acute sinusitis rate for all studied biologics, despite lower values enregistered at T6 for the anti-IL5/R and anti-IL4R groups. Anti-IL4R showed higher effectiveness to improve the NP endoscopic score compared to anti-IL5/R and anti-IgE. Similarly, the LMS was lower in the anti-IL4R group at T6, but the changes were not significantly different between the groups. The anti-IL5/R group had a greater reduction of BEC at T6 compared to the other groups (Tables 2 and 5).

The comparative analysis between the subgroups treated by anti-IL5 and anti-IL5R antibodies showed a better effectiveness for the second one to improve the exacerbation rate, FVC, LMS and BEC after 6 months of treatment (Table 3).

When the OR were calculated to estimate the success of the biologics at 6 months to improve SAA and NP outcomes with the anti-IgE as reference, we found that the anti-IL4R antibody is the best therapy to improve the smell (OR 7.5 [2.1–35.8]), nasal obstruction (OR 12.0 [2.0–23.1]), VAS total ENT symptoms score (OR 3.3 [0.1–16.4]), night asthma attacks (OR 15.1 [2.7–28.5]), and NP endoscopic score (OR 18.1 [4.5–24.5]). The anti-IL5/R antibodies seem to be more effective to reduce SABA use per week (OR 3.8 [1.4–11.6]) and BEC (OR 13.5 [4.5–45.7]), but less efficient that the anti-IgE biotherapy to reduce nasal pruritus and sneezing (Table 6). There was no significant difference between biologics concerning the criteria of asthma exacerbations decrease by $\geq$ 50 %.

4. Discussion

This real-world study showed a similar effectiveness for anti-IgE, anti-IL5/R and anti-IL4R antibodies in patients with SAA eligible for all these biologics, having NP as comorbidity, in improving asthma symptoms, exacerbation rate, lung function parameters, but also the number of acute sinusitis and sinus imaging score after 6 months of treatment. However, anti-IL4R therapy has higher chances to reduce night asthma attacks, to improve the smell, nasal obstruction, VAS, and NP endoscopic scores, while anti-IL5/R antibodies have shown greater benefits to decrease SABA use per week and BEC, but lower effectiveness to reduce the nasal pruritus and sneezing compared to anti-IgE treatment.

The clinical utility of biologics for severe asthma has been well demonstrated in multiple randomized controlled trials (RCTs) and confirmed by real-world studies [1,8,23]. The anti-IgE antibody was the first biologic approved as add-on therapy for moderate-to-severe allergic

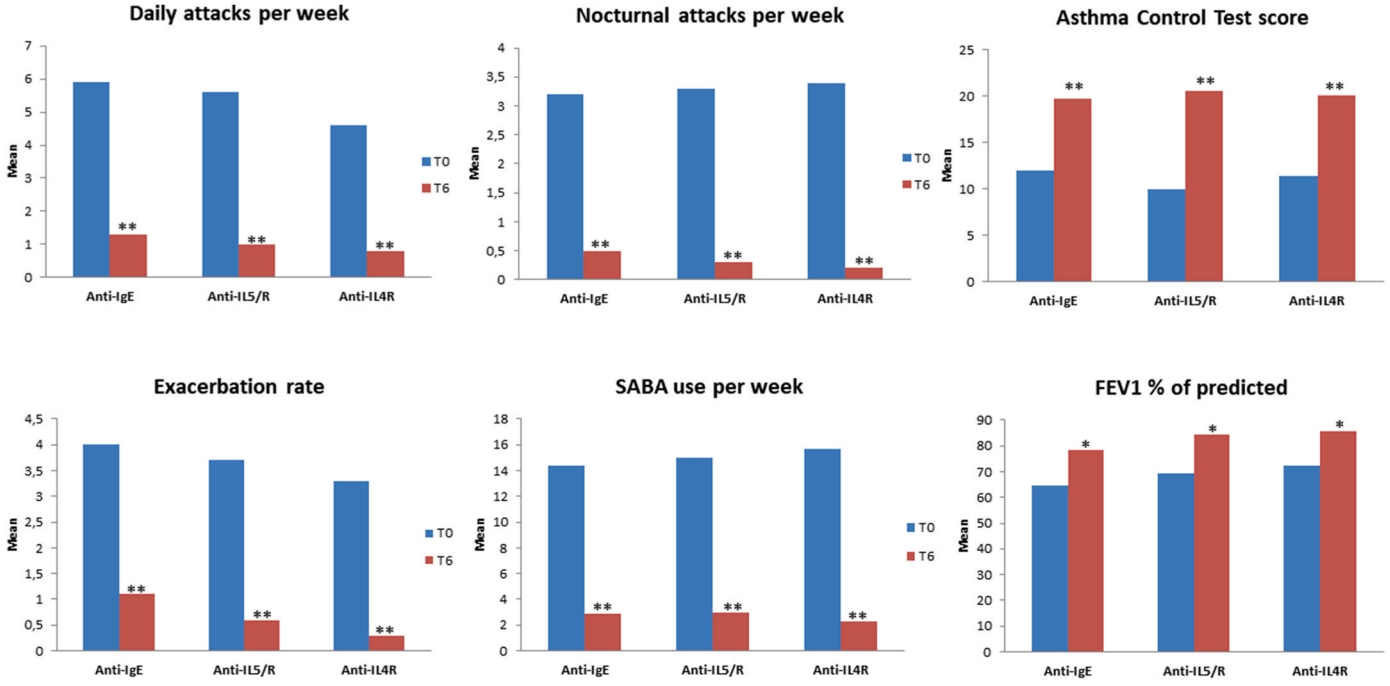

Fig. 1. Asthma outcomes at baseline (T0) and after 6 months of treatment (T6)
SABA: short-acting beta-2 adrenoceptor agonists; FEV1: Forced Expiratory Volume in 1s (% of predicted); * <0.05; ** <0.001.

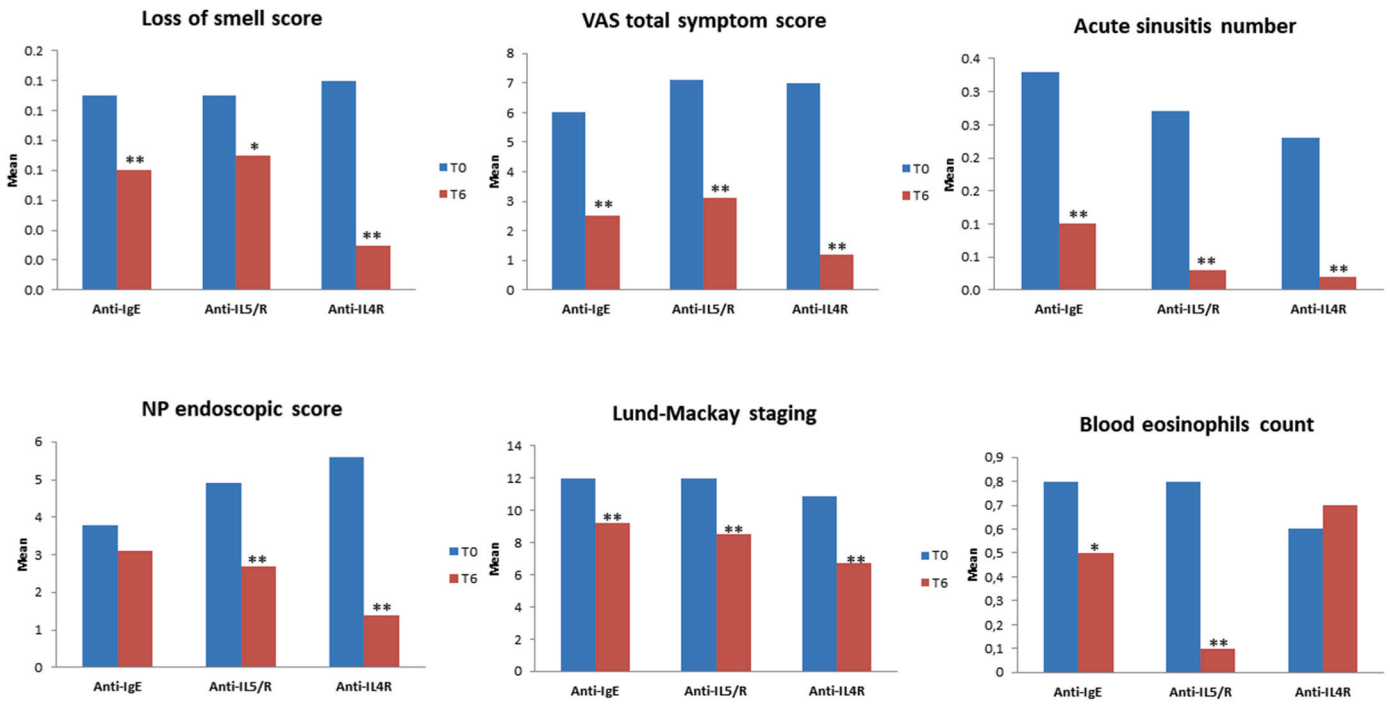

Fig. 2. Nasal polyps' outcomes and blood eosinophil count at baseline (T0) and after 6 months of treatment (T6)
VAS: visual analog scale; NP: nasal polyps; * <0.05; ** <0.001.

Table 5
Changes in outcomes parameters 6 months after treatment compared to baseline (Δ = T6-T0).

Parameter	Group 1 Anti-IgE N = 35	Group 2 Anti-IL5/R N = 38	Group 3 Anti-IL4R N = 34	1 vs 2 p-value	2 vs 3 p-value	1 vs 3 p-value	p-value
Δ Dyspnoea MMRC, mean (SD)	−1.3 (0.9)	−1.2 (0.9)	−1.2 (1.0)	0.535	0.765	0.365	0.653
Δ Daily attacks, mean (SD)	−4.6 (3.1)	−4.6 (2.9)	−3.8 (2.6)	0.938	0.185	0.212	0.336
Δ Nocturnal attacks, mean (SD)	−2.7 (1.8)	−3.0 (1.9)	−3.2 (2.6)	0.211	0.686	0.354	0.420
Δ ACT score, mean (SD)	7.8 (4.0)	10.6 (4.9)	8.7 (4.8)	**0.014**	0.118	0.518	**0.049**
Δ Exacerbations, mean (SD)	−2.9 (1.3)	−3.1 (1.3)	−3.0 (1.4)	0.534	0.113	0.303	0.270
Δ SABA use, mean (SD)	−11.5 (7.3)	−12.0 (6.3)	−13.4 (8.1)	0.727	0.690	0.399	0.723
Δ LoS score, mean (SD)	−0.6 (0.7)	−0.5 (0.6)	−1.1 (0.7)	0.523	**<0.001**	**0.001**	**0.001**
Δ VAS score, mean (SD)	−3.5 (1.9)	−4.0 (2.4)	−5.8 (1.4)	0.314	**<0.001**	**<0.001**	**<0.001**
Δ Sinusitis, mean (SD)	−2.3 (1.7)	−2.4 (1.4)	−2.1 (1.2)	0.668	0.052	0.198	0.156
Δ LMS, mean (SD)	−2.8 (2.7)	−3.5 (2.8)	−4.1 (2.7)	0.650	0.149	0.071	0.158
Δ NP endoscopic score, mean (SD)	−0.7 (1.2)	−2.2 (1.8)	−4.1 (1.5)	**<0.001**	**<0.001**	**<0.001**	**<0.001**
Δ FEV1 (%), mean (SD)	13.5 (14.8)	14.9 (14.3)	13.3 (12.0)	0.443	0.291	0.888	0.569
Δ FVC (%), mean (SD)	12.2 (17.2)	14.0 (16.9)	7.4 (13.5)	0.456	0.099	0.380	0.258
Δ FEV1/FVC (%), mean (SD)	3.8 (8.3)	4.5 (7.3)	6.2 (10.9)	0.692	0.461	0.324	0.728
Δ BEC (× 10^9/L), mean (SD)	−0.3 (0.3)	−0.7 (0.4)	0.1 (0.8)	**<0.001**	**<0.001**	**0.001**	**<0.001**

IgE: immunoglobulin E; IL5/R: interleukin 5/5 receptor; IL4R: inteleukin 4 receptor; SD: standard deviation; MMRC: modified Medical Research Council scale; ACT: Asthma Control Test; SABA: Short-Acting Beta-Agonists; LoS: loss of smell; VAS: visual analog scale; LMS: Lund-Mackay staging; NP: nasal polyps; FEV1: Forced Expiratory Volume at the end of the first second; FVC: Forced Vital Capacity; BEC: blood eosinophil count.

asthma [1]. In line with previous real-word data, the present study showed undeniable benefits of the anti-IgE in SAA by the amelioration of respiratory symptoms, asthma control, lung function and by the reduction of exacerbation rate, asthma attacks and rescue medication use [24,25]. Even though the anti-IL5/R antibodies are indicated in severe eosinophilic asthma, they proved similar effects in allergic and non-allergic patients in real-world setting [26,27]. Our results confirmed the effectiveness of the anti-IL5/R antibodies in SAA by improving almost all the studied parameters. Compared to the anti-IgE, in our study, the anti-IL5/R had greater benefits on asthma control, and decrease of SABA use ≤2/week, but failed to show its superiority on the exacerbation rate as recently found in a large real-world cohort with patients eligible for both biological classes [8]. However, the rate of exacerbation was significantly lower at 6 months in the anti-IL5/R group compared to the anti-IgE group, so the difference could be related to the shorter time of assessment in the present study than in the other one (12 months). The effect on the exacerbation rate seems to be higher in the anti-IL5R group than in the anti-IL5 after 6 months of treatment. Like the other biologics taken into the study, the anti-IL4R antibody was effective to improve the exacerbation rate, symptom control and FEV1 in patients with SAA. Despite that the effectiveness of the anti-IL4R treatment was not previously evaluated specifically in SAA in real-world setting, our findings are in line with the results recently published from a Dutch cohort including type-2 severe asthma patients [28]. In addition, subgroups analyses from previous studies showed similar effectiveness of the anti-IL4R antibody in type-2 severe asthma patients with and without allergic background [29–31]. There were no significant differences concerning the changes in asthma outcomes between the

Table 6
Odds ratios of success of biologics on study parameters after 6 months of treatment.

Parameter			Univariate analysis		Multivariate analysis	
	Biologic	Success n(%)	OR (CI95 %)	p-value	OR (CI95 %)	p-value
Pruritus	Anti-IgE	16 (46)	1			
	Anti-IL5/R	4 (11)	0.02 (0.00–0.11)	**<0.001**		
	Anti-IL4R	12 (35)	0.19 (0.01–1.47)	0.157		
Smell	Anti-IgE	18 (51)	1			
	Anti-IL5/R	18 (47)	0.88 (0.34–2.29)	0.797		
	Anti-IL4R	27 (79)	7.50 (2.11–35.80)	**0.004**		
Rhinorrhea	Anti-IgE	25 (71)	1			
	Anti-IL5/R	23 (61)	0.75 (0.26–2.14)	0.595		
	Anti-IL4R	29 (85)	2.61 (0.75–10.60)	0.146		
Sneeze	Anti-IgE	19 (54)	1			
	Anti-IL5/R	12 (32)	0.17 (0.03–0.68)	**0.019**		
	Anti-IL4R	12 (35)	0.42 (0.08–1.87)	0.270		
Nasal obstruction	Anti-IgE	22 (34)	1			
	Anti-IL5/R	28 (74)	1.13 (0.37–3.44)	0.827		
	Anti-IL4R	33 (97)	12.00 (2.00–23.10)	**0.023**		
LoS score increase by ≥0.5	Anti-IgE	18 (51)	1			
	Anti-IL5/R	18 (53)	0.85 (0.34–2.13)	0.729		
	Anti-IL4R	27 (79)	3.64 (1.30–11.10)	**0.017**		
VAS reduction ≥2 cm	Anti-IgE	30 (86)	1			
	Anti-IL5/R	13 (34)	0.67 (0.22–2.01)	–		
	Anti-IL4R	34 (100)	3.32 (0.13–16.40)	–		
Dyspnoea	Anti-IgE	13 (37)	1			
	Anti-IL5/R	13 (34)	0.96 (0.36–2.53)	0.928		
	Anti-IL4R	9 (26)	0.66 (0.23–1.84)	0.434		
Cough	Anti-IgE	15 (43)	1			
	Anti-IL5/R	21 (55)	1.60 (0.60–4.31)	0.345		
	Anti-IL4R	19 (56)	2.25 (0.79–6.70)	0.134		
Daily attacks ≤2/week	Anti-IgE	29 (83)	1			
	Anti-IL5/R	33 (87)	1.37 (0.37–5.19)	0.635		
	Anti-IL4R	32 (94)	3.31 (0.70–23.80)	0.162		
Night attacks none/week	Anti-IgE	24 (69)	1			
	Anti-IL5/R	33 (87)	3.03 (0.97–10.70)	0.066		
	Anti-IL4R	33 (97)	15.10 (2.67–28.6)	**0.012**		
SABA use ≤2/week	Anti-IgE	18 (51)	1			
	Anti-IL5/R	30 (79)	3.81 (1.36–11.60)	**0.014**		
	Anti-IL4R	23 (68)	2.27 (0.83–6.52)	0.116		
ACT score ≥20	Anti-IgE	20 (57)	1			
	Anti-IL5/R	28 (74)	2.10 (0.79–5.76)	0.140		
	Anti-IL4R	22 (65)	1.37 (0.52–3.68)	0.520		
Δ ACT score ≥3	Anti-IgE	32 (91)	1			
	Anti-IL5/R	36 (95)	1.69 (0.26–13.4)	0.580		
	Anti-IL4R	30 (88)	0.70 (0.13–3.44)	0.662		
Asthma Exacerbations	Anti-IgE	32 (91)	1		1	
Decrease by ≥50 %	Anti-IL5/R	37 (97)	3.47 (0.42–72.0)	0.292	7.12 (0.61–22.0)	0.164
	Anti-IL4R	33 (97)	3.09 (0.37–64.30)	0.339	4.10 (0.36–10.8)	0.295
Acute Sinusitis	Anti-IgE	25 (71)	1			
Decrease by ≥50 %	Anti-IL5/R	34 (89)	3.40 (1.01–13.60)	0.059		
	Anti-IL4R	28 (82)	1.87 (0.60–6.19)	0.286		
Δ LMS ≥5	Anti-IgE	8 (23)	1			
	Anti-IL5/R	10 (26)	1.20 (0.40–3.65)	0.746		
	Anti-IL4R	13 (38)	2.20 (0.76–6.70)	0.153		
Δ NP endoscopic score ≥1	Anti-IgE	19 (54)	1			
	Anti-IL5/R	31 (82)	3.32 (1.34–9.02)	–		
	Anti-IL4R	34 (100)	18.10 (4.48–24.50)	–		
Δ FEV1 >10 %	Anti-IgE	16 (46)	1			
	Anti-IL5/R	23 (61)	1.82 (0.72–4.69)	0.207		
	Anti-IL4R	19 (56)	1.50 (0.58–3.93)	0.399		
Δ FVC >10 %	Anti-IgE	13 (37)	1			
	Anti-IL5/R	22 (58)	2.33 (0.92–6.08)	0.078		
	Anti-IL4R	14 (41)	1.18 (0.45–3.15)	0.732		
BEC < 0.15× 10^9/L	Anti-IgE	6 (17)	1			
	Anti-IL5/R	28 (74)	13.50 (4.6–45.7)	**<0.001**		
	Anti-IL4R	5 (15)	0.83 (0.22–3.07)	0.782		

IgE: immunoglobulin E; IL5/R: interleukin 5/5 receptor; IL4R: inteleukin 4 receptor; OR: odds ratio; CI: confidence interval; LoS: loss of smell; VAS: visual analog scale; MMRC: modified Medical Research Council scale; SABA: Short-Acting Beta-Agonists; ACT: Asthma Control Test; LMS: Lund-Mackay staging; NP: nasal polyps; FEV1: Forced Expiratory Volume at the end of the first second; FVC: Forced Vital Capacity; BEC: blood eosinophil count.

anti-IL5/R and anti-IL4R groups.

Concerning the NP, all the studied biologics improved nasal symptoms, LoS score, VAS total symptom score, LMS and decreased the number of acute sinusitis per six months, so implicitly the systemic corticosteroids use, as already reported by RCTs and several real-world studies [19,32–37]. As previously showed, all the biologics decreased the NP endoscopic score, but the results reached significance in our study only for the groups treated by anti-IL5/R and anti-IL4R [19,32,33]. Despite that the anti-IgE antibody seems to be less effective in reducing the NP size in the present study, we should interpret this result

by also considering that at baseline the mean endoscopic score was significantly lower in this group compared to the others. The comparative analysis in changes of ENT parameters showed a better effectiveness of the anti-IL4R antibody in improving the LoS, VAS total symptom and NP endoscopic scores than the other biologics taken into study. These benefits were already suggested by indirect comparisons realized on previous studies that evaluated the effectiveness of biologics on NP [32,33,35,36].

The originality of this work consists in the real-world head-to-head comparison in terms of effectiveness of three different biological classes in SAA associated with NP, an overlapping phenotype sharing characteristics of IgE-mediated disease with those related to the presence of severe eosinophilic inflammation in the airways. According to our results, this population has several particularities: adult-onset of asthma, predominance of never-smokers (both characteristics already described in severe asthma cohorts), preponderance of men, high rate of previous NP surgery (more specific for NP), high levels of BEC (typical for severe eosinophilic asthma and NP) and increased IgE serum levels (related to the allergic background) [4,14,17]. The distribution of the aeroallergens sensitizations in this study is typical for Western Europe [6,38]. The higher prevalence of the pollens sensitization in the group treated by anti-IL4R antibody could be explained by the benefits proved of this treatment in patients with allergic background and the restriction of anti-IgE prescriptions only in patients with sensitization to at least one perennial allergen [29,38]. Viewing the clinical and biological characteristics of patients with SAA-NP, they are eligible for more biological classes, so head-to-head comparisons are very important and could help us in clinical practice. Unfortunately, in the SAA-NP association, except for our previous study, there is no other data available for comparison [13]. Our findings on the effectiveness on SAA parameters of different biologics are similar (like in our previous study [13]), but the anti-IL4R antibody, not studied in the precedent analysis, showed undeniable superiority compared to the others concerning NP outcomes. According to our criteria of response, with the anti-IgE antibody as reference, the biologics taken into the study showed similar effectiveness in improving asthma outcomes (symptoms, exacerbation rate, asthma control, lung function) with a superiority found for the anti-IL4R antibody in terms of amendment of night attacks and for the anti-IL5/R in decreasing the SABA use per week. The great response to treatment in our population is probably related to the presence of NP as comorbidity, well recognized now as a predictor of the effectiveness of biologics in SA in RCTs and real-world setting [17,39]. More differences were registered in our study for the sino-nasal outcomes. Despite the improvement of almost all rhinological parameters and sinus imaging in each group, greater benefits were found in the group treated by the anti-IL4R antibody in terms of LoS, nasal obstruction, VAS total symptom score and NP endoscopic size. Our results of the comparison are in line with other previous data from two real-world studies including patients with severe asthma and NP [12,40]. However, the most effective biologic in improving nasal pruritus and sneezing, symptoms more related to allergic rhinitis than to NP was the anti-IgE antibody. These are expected findings because allergic rhinitis is an IgE-mediated disease and this biologic previously proved its effectiveness to treat this condition by reducing not just the nasal symptoms but also the daily rescue antihistamines use, and by increasing the related-quality of life [41]. In line with previous data, the anti-IL4R treatment also showed a certain effectiveness in improving both these symptoms in contrast with the anti-IL5/R antibodies [42]. Similarly, viewing their mechanisms of action, the anti-IL5/R antibodies demonstrated greater reduction of BEC compared to the other studied biologics [17].

Limitations of our study include a retrospective design, restrained number of patients, lack of baseline homogeneity with different preexistent states of asthma/NP control between the treatment groups that could add difficulty in deriving conclusions about which biologic is more efficient at a specific outcome. Strengths of our study are the head-to-head comparison in terms of effectiveness between three different biological classes, the similar size of groups, the large number of variables analyzed for the correct assessment of respiratory and nasal outcomes and the use of well-defined criteria of response to treatment.

This study showed comparable effectiveness of all three biological classes in SAA associated with NP by improving asthma outcomes. Despite an amelioration of almost all sino-nasal parameters by the biologics, some differences in treatment effects were found with greater benefits on NP outcomes in patients treated by anti-IL4R antibody, while patients receiving the anti-IgE therapy have more chances for an amendment of their nasal allergic symptoms. The anti-IL5/R antibodies are the most effective in reducing blood eosinophilic inflammation. These findings should be considered in the choice of the most adequate biologic agent for each patient in the era of personalized medicine. Larger head-to-head comparative studies are needed to validate our results.

CRediT authorship contribution statement

Angelica Tiotiu: Writing – review & editing, Writing – original draft, Validation, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Nicolas Migueres:** Formal analysis. **Francisco-Javier Gonzalez-Barcala:** Writing – review & editing, Validation, Investigation, Formal analysis, Data curation. **Pauline Roux:** Writing – review & editing, Validation, Data curation. **Jean-Philippe Oster:** Writing – review & editing, Validation, Data curation. **Natacha Moutard:** Writing – review & editing, Validation, Data curation. **Frederic de Blay:** Writing – review & editing, Validation, Investigation. **Philippe Bonniaud:** Writing – review & editing, Validation, Investigation, Data curation.

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Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Angelica Tiotiu reports a relationship with AstraZeneca, GSK, Sanofi that includes: board membership, consulting or advisory, and speaking and lecture fees.

Nicolas Migueres reports a relationship with AstraZeneca that includes speaking and lecture fees.

Francisco-Javier Gonzalez-Barcala reports a relationship with ALK, AstraZeneca, Bial, Chiesi, Gebro Pharma, GSK, Menarini, Rovi, Roxall, Sanofi, Stallergenes Greer, Teva that includes: board membership, consulting or advisory, and speaking and lecture fees.

Pauline Roux reports a relationship with AstraZeneca, GSK, Sanofi that includes: board membership, speaking and lecture fees.

Jean-Philippe Oster reports a relationship with AstraZeneca, GSK, Sanofi that includes: speaking and lecture fees.

Natacha Moutard reports a relationship with ASV that includes: attending meetings.

Frédéric de Blay reports a relationship with Aimmune, ALK, GSK, Regeneron, Stallergenes Greer that includes: grants, speaking and lecture fees.

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