Clinical Reviews in Allergy & Immunology
https://doi.org/10.1007/s12016-022-08938-w

Real-Life Effectiveness of Benralizumab, Mepolizumab and Omalizumab in Severe Allergic Asthma Associated with Nasal Polyps

Angelica Tiotiu[1,2] · Paula Mendez-Brea[3] · Iulia Ioan[2,4] · Rodrigo Romero-Fernandez[5] · Jean Philippe Oster[6] · Thi-cam-tu Hoang[6] · Pauline Roux[7] · Diana Carolina Ochoa-Gutierrez[8] · Philippe Bonniaud[9,10,11] · Frederic de Blay[8,12] · Francisco-Javier Gonzalez-Barcala[13,14,15]

Accepted: 7 April 2022
© The Author(s), under exclusive licence to Springer Science+Business Media, LLC, part of Springer Nature 2022

Abstract

Biological therapies are available for the treatment of the severe allergic asthma (SAA) with blood eosinophil count $\geq 0.3 \times 10^9$/L. Several of them also showed benefits on nasal polyps (NP), one of the most frequent comorbidities of the severe asthma, but comparative studies on their effectiveness in the association SAA-NP are currently lacking. The aim of this study is to compare the effectiveness of benralizumab, mepolizumab and omalizumab in patients with SAA-NP in real-life settings. A retrospective, observational, multicenter real-life study was realized including patients with SAA-NP treated by benralizumab, mepolizumab or omalizumab for 6 months. We analysed 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. Seventy-two patients with SAA-NP were included: 16 treated by benralizumab, 21 by mepolizumab and 35 by omalizumab. After 6 months of treatment, almost all studied parameters were improved (except sinus imaging) with a greater effect of omalizumab on the nasal pruritus ($p = 0.001$) and more benefits of benralizumab on exacerbations rate, asthma attacks per week and lung function (all $p < 0.05$). Benralizumab and mepolizumab were more effective to improve the NP endoscopic score and the blood eosinophil count (both $p < 0.001$). All three biological therapies showed effectiveness by improving asthma and nasal outcomes in patients with SAA-NP. Several differences have been found that should be confirmed by larger comparative studies.

Keywords Severe allergic asthma · Nasal polyposis · Biological therapies · Effectiveness · Comparative analysis

Abbreviations

ICS	Inhaled corticosteroids
LABA	Long-acting β2 receptors agonists
CS	Systemic corticosteroids
IgE	Immunoglobulin E
BEC	Blood eosinophil count
IL-5	Interleukin 5
IL-5R	Interleukin 5 receptor
IL-4	Interleukin 4
NP	Nasal polyps
SAA	Severe allergic asthma
ENT	Ear Nose Throat
SABA	Short-acting β2 receptors agonists
ACT	Asthma Control Test
FEV1	Forced expiratory volume in one second
FVC	Forced vital capacity
T0	At baseline
T6	After 6 months of treatment
CT	Computed tomography
OR	Odds ratios
GINA	Global Initiative for Asthma

Introduction

Severe asthma is a debilitating disease because of the presence of persistent uncontrolled symptoms (despite the adherence to high dose inhaled corticosteroids and long-acting β2 receptors agonists ICS-LABA, and the treatment of

✉ Angelica Tiotiu
angelica.tiotiu@yahoo.com

Extended author information available on the last page of the article

Published online: 14 April 2022

contributory factors and comorbidities) and frequent exacerbations (≥ 2/year) requiring systemic corticosteroids (CS) use. Although its prevalence is low (3.7% of adult asthmatics), the burden of severe asthma is very important owing to the poor quality of life of patients, significant morbidity and mortality, high rate of absenteeism at the working place and increased healthcare costs [1]. Severe allergic asthma (SAA) is a specific phenotype of the severe asthma diagnosed by the presence of clinically apparent allergic reaction and an immunoglobulin E (IgE) response to specific aeroallergens [2]. The phenotypic characterization of the severe asthma across the world showed that up to 70% of patients have allergic backgrounds [3, 4] and nearly half of them are criteria for eosinophilic asthma (blood eosinophil count BEC $\geq 0.3 \times 10^9$/L) [4, 5]. Fortunately, biological therapies targeting IgE (omalizumab), IL-5 (mepolizumab and reslizumab), IL-5 receptor (IL-5R) (benralizumab) and IL-4 receptor (dupilumab) were developed and showed effectiveness by improving severe asthma outcomes in patients with allergic background and eosinophilic inflammation [1].

One of the most frequent comorbidities of the severe asthma is nasal polyps (NP) found in almost 40% of Caucasian patients [3, 4] compared to only 4% in the general population [6]. Although not life-threatening, NP severely affects the quality of life of patients, contributes to the poor control of asthma, alters lung function, increases the risk of asthma exacerbations and has a significant socio-economic impact due to repeated surgery and use of CS [7–10]. Because NP is associated with type 2 inflammation with secretion of IL-4, IL-5, IL-13 and IgE, most biological therapies developed for severe asthma targeting these cytokines have shown to improve NP outcomes [11–14].

Comparative studies on the effectiveness of biological therapies in the association SAA and NP are currently lacking. The aim of this study was to compare the effectiveness of omalizumab, mepolizumab and benralizumab in patients with SAA and NP in real-life settings.

Methods

Study Design and Participants

We realized a binational, multicenter, observational, real-life, pilot study in the Departments of Pulmonology of University Hospitals of Besançon, Dijon, Nancy and Strasbourg and the Regional Hospital of Colmar, France and Santiago de Compostela, Spain, from December 1, 2016, to July 31, 2021. The study was approved by the Institutional Review Board of the French learned society for respiratory medicine—Société de Pneumologie de Langue Française (CEPRO 2020–078) and the Santiago and Lugo Research and Ethics Committee (number 2019/438). All patients provided informed consent before extracting and using their data.

Hospital chest physicians with experience in treating severe asthma were asked to provide data of all their patients with SAA documented as clinically apparent allergic reaction and IgE response to at least one aeroallergen with associated NP treated by biological agents (omalizumab, benralizumab and mepolizumab) for at least 6 months. Each chest physician chose the biological therapy for its patients according to the individual clinical and biological criteria, but also the availability of the biologics in his country. The inclusion criteria were as follows: adult patients with SAA uncontrolled despite a step 5 treatment according to Global Initiative of Asthma (GINA) guideline having criteria for the instauration of a biological therapy [1] not previously treated by such treatment with associated NP diagnosed by an Ear Nose Throat (ENT) specialist receiving daily nasal corticosteroids without local antihistamines. The atopy was confirmed by skin prick tests to common aeroallergens according to the European standards [15] and the sensitization to at least one perennial allergen was documented before starting the treatment by omalizumab. All patients received a treatment by systemic antihistamines once daily for their symptoms related to allergic rhinitis.

The study patients were divided into three groups according to the chosen biological therapy: group 1 treated by subcutaneous mepolizumab 100 mg every 4 weeks, group 2 by subcutaneous benralizumab 30 mg every 8 weeks (after the three first doses every 4 weeks) and group 3 by subcutaneous omalizumab administrated every 2 or 4 weeks based on total serum IgE levels (UI/mL) and body weight (in kilograms), with a maximum dose of 600 mg every 2 weeks. A documented physician evaluation of response to biological therapy at 6 months of treatment was recorded from electronic patient files.

Outcome Measures

For asthma outcomes, we analysed clinical parameters (dyspnoea, cough, number of daytime asthma symptoms/week, number of nocturnal asthma symptoms/week, number of short-acting β2 receptors agonists (SABA) rescue/week, number of moderate/severe exacerbations), Asthma Control Test (ACT) score and lung function variables (forced expiratory volume in one second, FEV1; forced vital capacity, FVC; and FEV1/FVC ratio) measured according to the standardized methods [16], 6 months before (T0) and after the biological therapy (T6). ACT ≥ 20 was considered well-controlled asthma, ACT < 20 as poorly controlled asthma and change of ≥ 3 points clinically important in an individual patient [17]. Moderate/severe asthma exacerbation was defined as aggravation of respiratory symptoms requiring CS for ≥ 3 days and/or hospitalization.

The ENT evaluation included symptoms (pruritus, loss of smell, rhinorrhoea, sneezing, nasal obstruction), number of acute sinusitis episodes, sinus computed tomographic (CT) images and endoscopic evaluation of NP score 6 months before (T0) and after the biological therapy (T6). The endoscopic NP score was assessed by mean of endoscopy for each nostril separately and graded based on polyp size, resulting in scores of 0 to 4: 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 [18]. Acute sinusitis was defined as the presence of symptoms/signs such as discoloured discharge and purulent secretion in cavum nasi, severe local pain and fever (> 38 °C) for ≥ 5 days requiring antibiotics.

The single biomarker studied was the BEC, measured at T0 and T6.

Statistical Analysis

Statistical analysis was performed using the SPPS program version (SAS Institute, Cary, NC, USA) and Stata 15 [version 15.0, StataCorp LLC, College Station, TX, USA)]. Qualitative variables in descriptive analysis are expressed as number (percentage). Quantitative variables are presented as mean ± standard deviation (SD). Comparisons of values between two groups, i.e. group 1 vs group 2, group 2 vs group 3, group 1 vs group 3, were performed using non-parametric test Wilcoxon-Mann–Whitney or Fisher's exact test as needed, and between the three groups using non-parametric Anova, i.e. Kruskal–Wallis test or Fisher's exact test as needed, as the distribution was not normal. The comparison of variables between T0 and T6 after treatment by biological therapy was performed using Wilcoxon test for paired samples or Fisher's exact test as needed. The limit of significance was $p < 0.05$.

To check the response to different biological therapies between T0 and T6 (Δ = values at 6 months minus baseline values), we compared the differences in terms of symptoms, exacerbations, lung function parameters, asthma control, number of acute sinusitis episodes, sinus imaging and BEC between the three groups of treatment. As statistical test, a non-parametric test Wilcoxon-Mann–Whitney was used for the comparison between two groups, respectively, a non-parametric Anova, i.e. Kruskal–Wallis test, for the comparison between the three groups. As sample size was scarce, we finally pooled in one unique group these subjects treated with mepolizumab and benralizumab (both anti-IL5 pathway). We considered success any change in the respiratory and ENT symptoms from 'severe' to 'inexistent' or 'normal' between T0 and T6. We considered failure any progression in the symptoms from 'severe' to 'severe' or from 'normal' to 'severe' between T0 and T6. Any progression from 'normal' to 'normal' or 'inexistent' to 'inexistent' was labelled as missing data and was not considered further. The success for asthma control at T6 was defined as ≤ 2 day attacks/week, none night attacks/week, SABA use ≤ 2/week, an ACT score ≥ 20 and/or ACT improvement ≥ 3 points from T0 to T6. A decrease of asthma exacerbation rate ≥ 1 per 6 months was considered a success. Conversely, the failure was defined if these criteria were not met. For the lung function variables, the success was defined as an increase > 12% of FEV1 or FVC between T0 and T6 or FEV1/FVC > 70% while failure was defined as any lower increase, any decrease or non-modification of the parameter. The increase was calculated as follows: [(value at T6—value at T0) × 100]/value at T0. For the ENT parameters, the success was defined as a reduction of the number of acute sinusitis episodes ≥ 1 per 6 months, and/or of the endoscopic NP stage ≥ 1 and/or improvement of sinus CT imaging at 6 months. In contrast, the failure was registered if one of these criteria was not met. For eosinophils, the success was defined as a decrease ≥ 80% of the count, calculated as (BEC at T6—BEC at T0)/BEC at T0. Any other change was considered failure. Furthermore, a second analysis for the absolute number of BEC at T6, regardless of their count at T0, was undertaken: a count of eosinophils $\leq 0.1 \times 10^9$/L was considered success and any other count was considered failure.

For each analysis, using binary logistic regression, we computed crude odds ratios (OR) as an estimate of the relative risk of failure. The outcome was 'failure' and the exposure was the treatment group (omalizumab versus mepolizumab and benralizumab). Due to the fact that only a small sample was available, the ORs were not adjusted for confounding variables and only crude estimates were considered.

Results

Population Characteristics at Baseline (T0)

Seventy-two patients with SAA and NP with a mean age of 53 ± 13 years were included. More than half of patients were males and the majority had adult-onset asthma (Table 1). Most of patients were non-smokers, with previous NP surgery and high serum levels of IgE. All the patients were allergic without significant differences between groups for the aeroallergens or the aspirin intolerance. There were no significant differences between the groups for the respiratory symptoms, the number of acute sinusitis, SABA use, lung function parameters and BEC (Tables 1 and 2). All the patients had airway obstruction without significant differences between groups. At baseline, the predominant ENT

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

Parameter	All patients ($N=72$)	Group 1 Mepolizumab ($N=21$)	Group 2 Benralizumab ($N=16$)	Group 3 Omalizumab ($N=35$)	p value (ANOVA)
Age, mean (SD)	53 (13)	53 (11)	56 (11)	51 (15)	0.683
Male, *n* (%)	42 (58%)	12 (57%)	8 (50%)	22 (63%)	0.764
Adult-onset asthma, *n* (%)	58 (81%)	18 (86%)	11 (69%)	29 (83%)	0.387
Family history, *n* (%)					
Asthma	20 (28%)	8 (38%)	8 (50%)	4 (11%)	0.008
Atopy	25 (35%)	11 (52%)	9 (56%)	5 (14%)	0.002
Previous polyp surgery, *n* (%)	45 (64%)	13 (62%)	9 (56%)	24 (69%)	0.679
Smoking history, *n* (%)					0.404
Never-smoker	51 (71%)	18 (86%)	11 (69%)	22 (63%)	
Ex-smoker	20 (28%)	3 (14%)	5 (31%)	12 (34%)	
Active-smoker	1 (1%)	0	0	1 (3%)	
Pack-years, mean (SD)	4 (7)	3 (7)	4 (6)	4 (7)	0.195
Sensitizations, *n* (%)					
House dust mite	54 (75%)	15 (71%)	10 (63%)	29 (83%)	0.269
Pets	24 (33%)	6 (29%)	5 (31%)	13 (37%)	0.789
Moulds	20 (28%)	6 (29%)	5 (31%)	9 (26%)	0.915
Pollens	30 (42%)	7 (33%)	9 (56%)	14 (40%)	0.361
Aspirin intolerance, *n* (%)	16 (22%)	4 (14%)	2 (13%)	10 (29%)	0.288
Total serum IgE, mean (SD) (UI/mL)	501.1 (462.1)	478.1 (580.9)	452.1 (332.3)	537.3 (442.6)	0.557

symptoms were loss of smell, rhinorrhoea and nasal obstruction, the last one more frequent in the benralizumab group (Table 2). The benralizumab group compared to the omalizumab group had lower ACT score (8.7 ± 3.5 vs 12.0 ± 3.8, $p=0.003$) and exacerbation rate during the 6 months preceding the inclusion (3.3 ± 1.4 vs 4.0 ± 1.4, $p=0.044$) (Table 2). The benralizumab and mepolizumab groups had more frequently familial history of asthma and atopy compared to the omalizumab group ($p \leq 0.002$, Table 1), more severe NP in endoscopy and frequently NP with sinusitis on the sinus CT scan than the omalizumab group ($p<0.05$, Table 2). Similar results were found when a comparison was realized between the mepolizumab and benralizumab group put together vs the omalizumab group. At baseline, the patients treated by an anti-IL5/R antibodies versus those treated by anti-IgE antibody had nasal obstruction as predominant symptom (97% vs 86%, $p=0.006$), higher NP score (5.0 ± 1.4 vs 3.8 ± 1.6, $p=0.001$), poorer asthma control (9.8 ± 3.7 vs 12.0 ± 3.8, $p=0.001$) and more frequently NP with sinusitis on the CT scan (97% vs 71%, $p=0.001$) (eTable 1).

Outcome Measures at T6

After 6 months of treatment, all groups significantly improved the respiratory symptoms and ACT score and decreased the number of asthma attacks/week, SABA use/week and asthma exacerbations/6 months (Table 3, Fig. 1). There were no significant differences between groups at T6 for dyspnoea and cough, but a greater improvement of the ACT score has been found in the benralizumab group compared to the other groups. Similarly, at T6, the benralizumab treatment seems to be more efficient compared to omalizumab and mepolizumab to decrease daily and nocturnal attacks/week, SABA use/week and the exacerbation number/6 months (Tables 2 and 4). However, the changes during treatment have not reached significance for the rate of exacerbations and SABA use (Table 4).

FEV1 and FVC were also improved for all patients, but a significant effect on the airway obstruction has been seen in the groups benralizumab (61.3% vs 67.8%, $p=0.002$) and omalizumab (63.4% vs 67.2%, $p=0.011$) (Table 3). Despite that the FEV1 values at T6 were similar, the changes were significant for the benralizumab group compared to the others ($p<0.03$, Table 4). Conversely, FVC was higher in the benralizumab group but its variation was not significantly different when compared to the omalizumab and mepolizumab groups (Tables 2 and 4).

At 6 months of treatment, all ENT symptoms were significantly improved, but the benefit on the sneeze and nasal pruritus was greater for the omalizumab group compared to the others (Tables 2, 3 and 4). Despite that the number of acute sinusitis episodes was significantly lower in the benralizumab group compared to omalizumab (0.1 ± 0.3 vs 1.0 ± 1.4, $p=0.004$, Table 2), the changes have not reached significance (Table 4). The mean of the endoscopic NP

Table 2 Characteristics of the study population at baseline (T0) and 6 months after biological therapy (T6) according to treatment group

Parameter	Group 1 Mepolizumab ($N=21$)	Group 2 Benralizumab ($N=16$)	Group 3 Omalizumab ($N=35$)	1 vs 2 p	1 vs 3 p	2 vs 3 p	p value ANOVA
	At baseline (T0)						
ENT symptoms, *n* (%)							
Pruritus	9 (43)	10 (63)	19 (54)	0.109	0.281	0.433	0.485
Loss of smell	18 (86)	16 (100)	33 (94)	0.076	0.381	0.206	0.373
Rhinorrhoea	17 (81)	16 (100)	34 (97)	0.265	0.210	0.848	0.130
Sneeze	10 (48)	12 (75)	22 (63)	0.141	0.266	0.589	0.522
Nasal obstruction	20 (95)	16 (100)	30 (86)	0.089	0.121	**0.004**	**0.047**
Respiratory symptoms							
Dyspnoea, mean MMRC (SD)	2.1 (0.9)	2.4 (0.8)	2.2 (0.9)	0.167	0.375	0.257	0.633
Cough, *n* (%)	20 (95)	14 (88)	29 (71)	0.407	0.489	0.927	0.664
Daily attacks/week, mean (SD)	5.2 (3.1)	6.2 (3.0)	5.9 (2.9)	0.145	0.195	0.363	0.529
Nocturnal attacks/week, mean (SD)	3.2 (2.1)	3.6 (1.7)	3.2 (2.0)	0.199	0.407	0.083	0.407
Acute sinusitis/6 months, mean (SD)	2.6 (1.6)	2.9 (1.3)	3.3 (2.1)	0.191	0.069	0.152	0.246
Exacerbations/6 months, mean (SD)	4.0 (1.9)	3.3 (1.4)	4.0 (1.4)	0.165	0.393	**0.044**	0.273
SABA use/week, mean (SD)	15.7 (10.3)	14.6 (7.5)	14.4 (7.3)	0.494	0.472	0.459	0.993
ACT score, mean (SD)	10.7 (3.6)	8.7 (3.5)	12.0 (3.8)	0.072	0.109	**0.003**	**0.019**
Lung function							
FEV1 (% predicted)	69.6 (24.6)	65.8 (17.5)	64.5 (17.4)	0.289	0.159	0.360	0.590
FVC (% predicted)	87.1 (24.8)	89.0 (13.3)	85.1 (15.7)	0.497	0.245	0.063	0.389
FEV1/FVC (%)	64.7 (10.9)	61.3 (14.3)	63.4 (13.2)	0.278	0.442	0.327	0.839
CT sinus scan, *n* (%)				0.295	**0.009**	**0.047**	**0.007**
Nasal polyps	0 (0)	1 (6)	10 (29)				
Nasal polyps + sinusitis	21 (100)	15 (94)	25 (71)				
Nasal polyps score, mean (SD)	4.8 (1.4)	5.5 (1)	3.8 (1.6)	0.370	**0.029**	**0.003**	**0.026**
BEC ($\times 10^9$/L)**,** mean (SD)	0.9 (0.4)	0.7 (0.4)	0.8 (0.5)	0.187	0.242	0.274	0.585
	After 6 months (T6)						
ENT symptoms, *n* (%)							
Pruritus	9 (43)	6 (38)	1 (3)	0.432	**< 0.001**	**0.004**	**0.001**
Loss of smell	12 (57)	11 (69)	21 (60)	0.745	0.731	0.751	0.887
Rhinorrhoea	10 (48)	8 (50)	24 (69)	0.859	0.122	0.364	0.296
Sneeze	7 (33)	4 (25)	4 (11)	0.583	**0.046**	0.216	0.133
Nasal obstruction	10 (48)	6 (38)	18 (51)	0.769	0.064	0.204	0.137
Respiratory symptoms							
Dyspnoea, mean MMRC (SD)	1.0 (1.1)	1.1 (0.9)	0.9 (0.8)	0.277	0.208	0.190	0.680
Cough, *n* (%)	10 (48)	4 (25)	16 (46)	0.160	0.890	0.160	0.306
Daily attacks/week, mean (SD)	1.5 (2.4)	0.5 (1.5)	1.3 (1.4)	0.078	0.225	**0.012**	0.052
Nocturnal attacks/week, mean (SD)	0.5 (1.1)	0.1 (0.5)	0.5 (0.9)	0.224	0.239	**0.039**	0.156
Acute sinusitis/6 months, mean (SD)	0.4 (0.7)	0.1 (0.3)	1.0 (1.4)	0.115	0.070	**0.004**	**0.021**
Exacerbations/6 months, mean (SD)	0.9 (1.2)	0.2 (0.4)	1.1 (1.4)	**0.016**	0.278	**0.003**	**0.017**
SABA use/week, mean (SD)	4.6 (8.4)	1.0 (3.0)	2.9 (3.1)	0.066	0.162	**0.002**	**0.024**
ACT score, mean (SD)	19.7 (4.8)	21.6 (4.1)	19.8 (3.4)	0.123	0.324	**0.015**	0.125
Lung function							
FEV1 (% predicted)	80.3 (20.8)	86.9 (19.2)	78.1 (18.8)	0.138	0.367	0.062	0.296
FVC (% predicted)	98.8 (22.7)	107 (21.4)	97.3 (21.8)	**0.036**	0.279	**0.012**	0.061
FEV1/FVC (%)	67.8 (8.4)	67.8 (12.0)	67.2 (10.0)	0.285	0.448	0.292	0.816

Table 2 (continued)

Parameter	Group 1 Mepolizumab ($N=21$)	Group 2 Benralizumab ($N=16$)	Group 3 Omalizumab ($N=35$)	1 vs 2 p	1 vs 3 p	2 vs 3 p	p value ANOVA
CT sinus scan, n (%)				0.258	**0.024**	0.235	0.532
Nasal polyps	1 (5)	3 (19)	11 (31)				
Nasal polyps + sinusitis	20 (95)	13 (81)	24 (69)				
Nasal polyps score, mean (SD)	3.0 (2.4)	3.0 (2.0)	3.4 (1.8)	0.346	0.063	0.656	0.188
BEC ($\times 10^9$/L)**,** mean (SD)	0.2 (0.2)	0.0 (0.0)	0.5 (0.3)	**< 0.001**	**< 0.001**	**< 0.001**	**< 0.001**

ENT, Ear Nose Throat; *MMRC*, modified Medical Research Council scale; *SD*, standard deviation; *SABA*, short-acting beta-agonists; *ACT*, Asthma Control Test; *FEV1*, forced expiratory volume at the end of the first second; *FVC*, forced vital capacity; *CT*, computed tomography; *BEC*, blood eosinophil count

score at T6 was similar for the three groups (Table 2), but the changes were more evident for the benralizumab group (Table 4). The difference between the mepolizumab and omalizumab groups on the sinus CT scan persists at T6 (Table 2). The benralizumab group had a significantly lower BEC at T6 (Table 2, Fig. 2) and a greater variation of this parameter compared to the others (Table 4).

Similar results were found when the analyses were done for the mepolizumab and benralizumab groups put together with a significant improvement of studied parameters (except the imaging) after 6 months of treatment (eTable 2). Significant differences were seen at T6 between the patients treated by anti-IgE and those treated by anti-IL-5/R antibodies, with greater improvement of nasal pruritus for the patients receiving omalizumab (3% vs 41%, $p<0.001$), but more important decrease of the number of acute sinusitis/6 months (0.3 ± 0.6 vs 1.0 ± 1.4, $p=0.006$) and the BEC (0.1 ± 0.2 vs 0.5 ± 0.3, $p<0.001$) for the mepolizumab or benralizumab group (eTable 1).

When the odds ratios (OR) were calculated to estimate the failure of the biological therapies at 6 months to improve SAA and NP outcomes with mepolizumab as reference, we found that omalizumab is the best therapy to improve nasal pruritus (OR 0.01 [0.00–0.11]) and sneezing (OR 0.09 [0.02–0.54]) while benralizumab is more effective to decrease the exacerbation rate, the number of acute sinusitis and the BEC. Conversely, compared to mepolizumab and benralizumab, omalizumab has more chances for failure in the reduction of SABA use (OR 4.05 [1.41–11.64]) and BEC (OR 25.21 [6.36–99.96]) (Table 5).

Discussion

The present study found that benralizumab, mepolizumab and omalizumab have similar effectiveness in patients with SAA and NP by reducing the asthma symptoms, improving lung function and sinus imaging at 6 months of treatment. However, benralizumab has higher chances to reduce the exacerbation rate and the numbers of acute sinusitis compared to the others, omalizumab has shown greater benefits on the nasal pruritus and sneezing, while benralizumab and mepolizumab seem more effective to decrease the NP scores and the BEC.

Omalizumab was the first biological therapy approved for the treatment of severe asthma and could be administrated in adults and children ≥ 6 years old with IgE-mediated moderate-to-severe persistent allergic asthma that remains uncontrolled despite GINA step 4 treatment, who have high levels of serum IgE, and at least a sensitization to a perennial allergen [17]. The current real-life study confirmed the effectiveness of omalizumab in SAA by improving the respiratory symptoms, asthma control and lung function and reducing the exacerbation rate, asthma attacks and rescue medication use (Table 3, Fig. 1) as previously described [18–20]. On the basis of two clinical trials POLYP 1 and POLYP 2 that showed significant benefits of omalizumab at 24 weeks on the nasal symptoms, endoscopic and Sino-Nasal Outcome Test-22 (SNOT-22) scores [13, 21], this treatment has been recently approved as medication for adults with NP uncontrolled despite nasal corticosteroids [22]. In addition to the improvement of the rhinorrhoea, nasal obstruction and sense of smell, our study found a significant decrease in the number of acute sinusitis episodes per 6 months, suggesting an implicit contribution in the sparing of CS demonstrated recently by a systematic review [23]. However, in the present study, the impact of omalizumab on the NP score did not reach statistical significance. The nasal symptoms related more to allergic rhinitis than to NP such as pruritus and sneezing have been also improved. These are expected findings because allergic rhinitis is an IgE-mediated disease and omalizumab already proved its effectiveness to treat this condition by improving not just the nasal symptoms but also the related quality of life and by reducing the daily rescue antihistamines use [24]. The effectiveness of omalizumab has been already studied in the association of SAA and NP in the real-world setting [25–28]. In line with these previous data, the present study demonstrated that omalizumab is an interesting therapeutic option able to treat both conditions in the same time.

Table 3 Comparative analysis of the study parameters at baseline (T0) and 6 months after biological therapy (T6) for each treatment group

Group	Parameter	At baseline	At 6 months	*p* value
Group 1 Mepolizumab (*N* = 21)	**ENT symptoms,** n (%)			
	Pruritus	9 (43)	9 (43)	1
	Loss of smell	18 (86)	12 (57)	**0.008**
	Rhinorrhoea	17 (81)	10 (48)	**< 0.001**
	Sneeze	10 (48)	7 (33)	**0.042**
	Nasal obstruction	20 (95)	10 (48)	**< 0.001**
	Respiratory symptoms			
	Dyspnoea, mean MMRC (SD)	2.1 (0.9)	1.0 (1.1)	**0.002**
	Cough, n (%)	20 (95)	10 (48)	**< 0.001**
	Daily attacks/week, mean (SD)	5.2 (3.1)	1.5 (2.4)	**< 0.001**
	Nocturnal attacks/week, mean (SD)	3.2 (2.1)	0.5 (1.1)	**< 0.001**
	Acute sinusitis/6 months, mean (SD)	2.6 (1.6)	0.4 (0.7)	**< 0.001**
	Exacerbations/6 months, mean (SD)	4.0 (1.9)	0.9 (1.2)	**< 0.001**
	SABA use/week, mean (SD)	15.7 (10.3)	4.6 (8.4)	**< 0.001**
	ACT score, mean (SD)	10.7 (3.6)	19.7 (4.8)	**< 0.001**
	Lung function			
	FEV1 (% predicted)	69.6 (24.6)	80.3 (20.8)	**0.003**
	FVC (% predicted)	87.1 (24.8)	98.8 (22.7)	**0.008**
	FEV1/FVC (%)	64.7 (10.9)	67.8 (8.4)	0.075
	CT sinus scan, *n* (%)			0.332
	Nasal polyps	0 (0)	1 (5)	
	Nasal polyps + sinusitis	21 (100)	20 (95)	
	Nasal polyps score, mean (SD)	4.8 (1.4)	3.0 (2.4)	**0.002**
	BEC ($\times 10^9$/L)**,** mean (SD)	0.9 (0.4)	0.2 (0.2)	**< 0.001**
Group 2 Benralizumab (*N* = 16)	**ENT symptoms,** *n* (%)			
	Pruritus	10 (63)	6 (38)	0.056
	Loss of smell	16 (100)	11 (69)	**0.001**
	Rhinorrhoea	16 (100)	8 (50)	**< 0.001**
	Sneeze	12 (75)	4 (25)	**< 0.001**
	Nasal obstruction	16 (100)	6 (38)	**< 0.001**
	Respiratory symptoms			
	Dyspnoea, mean MMRC (SD)	2.4 (0.8)	1.1 (0.9)	**< 0.001**
	Cough, *n* (%)	14 (88)	4 (25)	**< 0.001**
	Daily attacks/week, mean (SD)	6.2 (3.0)	0.5 (1.5)	**< 0.001**
	Nocturnal attacks/week, mean (SD)	3.6 (1.7)	0.1 (0.5)	**< 0.001**
	Acute sinusitis/6 months, mean (SD)	2.9 (1.3)	0.1 (0.3)	**< 0.001**
	Exacerbations/6 months, mean (SD)	3.3 (1.4)	0.2 (0.4)	**< 0.001**
	SABA use/week, mean (SD)	14.6 (7.5)	1.0 (3.0)	**< 0.001**
	ACT score, mean (SD)	8.7 (3.5)	21.6 (4.1)	**< 0.001**
	Lung function			
	FEV1 (% predicted)	65.8 (17.5)	86.9 (19.2)	**< 0.001**
	FVC (% predicted)	89.0 (13.3)	107 (21.4)	**< 0.001**
	FEV1/FVC (%)	61.3 (14.3)	67.8 (12.0)	**0.002**
	CT sinus scan, *n* (%)			0.333
	Nasal polyps	1 (6)	3 (19)	
	Nasal polyps + sinusitis	15 (94)	13 (81)	
	Nasal polyps score, mean (SD)	5.2 (1.0)	3.0 (2.0)	**< 0.001**
	BEC ($\times 10^9$/L)**,** mean (SD)	0.7 (0.4)	0.0 (0.0)	**< 0.001**

Table 3 (continued)

Group	Parameter	At baseline	At 6 months	*p* value
Group 3 Omalizumab (*N* = 35)	**ENT symptoms,** *n* (%)			
	Pruritus	19 (54)	1 (3)	**< 0.001**
	Loss of smell	33 (94)	21 (60)	**< 0.001**
	Rhinorrhoea	34 (97)	24 (69)	**< 0.001**
	Sneeze	22 (63)	4 (11)	**< 0.001**
	Nasal obstruction	30 (86)	18 (51)	**< 0.001**
	Respiratory symptoms			
	Dyspnoea, mean MMRC (SD)	2.2 (0.9)	0.9 (0.8)	**< 0.001**
	Cough, *n* (%)	29 (71)	16 (46)	**< 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**
	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**
	ACT score, mean (SD)	12.0 (3.8)	19.8 (3.4)	**< 0.001**
	Lung function			
	FEV1 (% predicted)	64.5 (17.4)	78.1 (18.8)	**< 0.001**
	FVC (% predicted)	85.1 (15.7)	97.3 (21.8)	**< 0.001**
	FEV1/FVC (%)	63.4 (13.2)	67.2 (10.0)	**0.011**
	CT sinus scan, *n* (%)			0.712
	Nasal polyps	10 (29)	11 (31)	
	Nasal polyps + sinusitis	25 (71)	24 (69)	
	Nasal polyps score, mean (SD)	3.8 (1.6)	3.4 (1.8)	0.070
	BEC ($\times 10^9$/L)**,** mean (SD)	0.8 (0.5)	0.5 (0.3)	**< 0.001**

ENT, Ear Nose Throat; *MMRC*, modified Medical Research Council scale; *SD*, standard deviation; *SABA*, short-acting beta-agonists; *ACT*, Asthma Control Test; *FEV1*, forced expiratory volume at the end of the first second; *FVC*, forced vital capacity; *CT*, computed tomography; *BEC*, blood eosinophil count

Mepolizumab is a biological therapy directed against IL-5 and has been approved as add-on treatment for patients ≥ 12 years old with severe eosinophilic asthma (a blood eosinophil count ≥ 0.15×10^9/L at the moment of first administration or ≥ 0.3×10^9/L in the past year) that remains uncontrolled despite GINA step 4 therapy with ≥ 2 exacerbations requiring CS in the previous year [29]. In the present study, mepolizumab significantly decreased the asthma exacerbation rate and the BEC and improved asthma control and lung function as already described [30, 31] but showed also other benefits by the reduction of respiratory symptoms (dyspnoea, cough), asthma attacks and SABA use per week. Concerning NP, our study found a significant improvement of the nasal symptoms (except pruritus) and a decrease of the endoscopic score and acute sinusitis number after 24 weeks of treatment (Table 3, Figs. 1 and 2). These results are in line with the findings of a very recent clinical trial that proved the benefits of mepolizumab on the NP by reducing the endoscopic score, the nasal obstruction, the risk for nasal surgery and the needs for CS use [14] allowing this product to be approved now as add-on maintenance treatment in adults with NP [29]. No previous data exists about the effectiveness of mepolizumab in the association SAA and NP. However, some analyses showed an improvement of SNOT-22 score concomitantly to asthma outcomes when mepolizumab has been administrated in patients with severe asthma and NP [32] and conversely an improvement of asthma control and the exacerbation rate when the treatment was used in patients with NP and comorbid asthma [14].

Benralizumab is a humanized monoclonal antibody selective for IL-5R alpha subunit that induces eosinophil apoptosis through the mechanism of antibody-dependent cell-mediated cytotoxicity involving natural killer cells approved as add-on treatment for patients with severe asthma

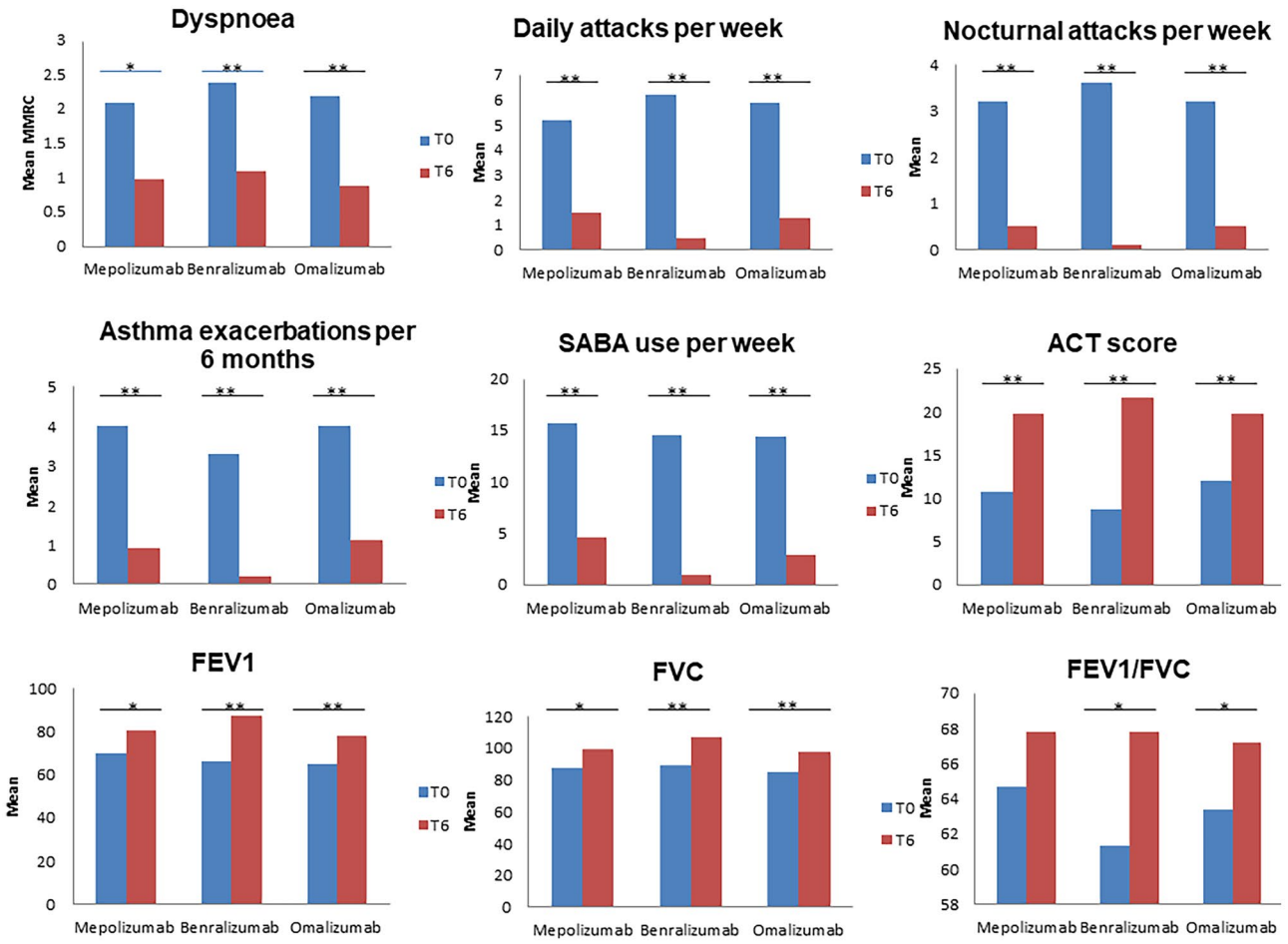

Fig. 1 Asthma outcomes at baseline (T0) and after 6 months of treatment (T6). SABA, short-acting beta-2 adrenoceptor agonists; ACT, Asthma Control Test score; FEV1, forced expiratory volume in 1 s (% of predicted); FVC, forced vital capacity (% of predicted)

Table 4 Changes in outcomes parameters 6 months after biological therapy compared to baseline (Δ = T6-T0)

Parameter	Group 1 $N=21$	Group 2 $N=16$	Group 3 $N=35$	1 vs 2 p	1 vs 3 p	2 vs 3 p	p value ANOVA
Δ Dyspnoea, mean (SD)	−1.1 (1.1)	−1.3 (0.8)	−1.3 (0.9)	0.286	0.472	0.426	0.697
Δ Daily attacks, mean (SD)	−3.8 (2.4)	−5.7 (3.3)	−4.6 (3.1)	**0.045**	0.407	0.210	0.157
Δ Night attacks, mean (SD)	−2.8 (1.9)	−3.5 (1.8)	−2.7 (1.8)	0.162	0.666	**0.039**	0.293
Δ SABA use, mean (SD)	−11.0 (5.5)	−13.6 (7.2)	−11.5 (7.3)	0.233	0.919	0.386	0.497
Δ Exacerbations, mean (SD)	−3.1 (1.3)	−3.1 (1.4)	−2.9 (1.3)	0.948	0.536	0.577	0.784
Δ ACT score, mean (SD)	9.0 (3.6)	12.9 (5.7)	7.8 (4.0)	**0.018**	0.262	**< 0.001**	**0.001**
Δ NP score, mean (SD)	−1.8 (1.0)	−1.8 (1.0)	−0.4 (0.2)	0.180	**0.020**	**< 0.001**	**< 0.001**
Δ Sinusitis, mean (SD)	−2.1 (1.5)	−2.8 (1.3)	−2.3 (1.7)	0.220	0.340	0.750	0.490
Δ BEC ($\times 10^9$/L), mean (SD)	−0.7 (0.4)	−0.7 (0.4)	−0.3 (0.3)	0.812	**< 0.001**	**< 0.001**	**< 0.001**
Δ FEV1 (%), mean (SD)	11.1 (15.0)	21.1 (12.3)	13.5 (14.8)	**0.028**	0.815	**0.021**	0.110
Δ FVC (%), mean (SD)	11.7 (18.0)	18.0 (15.5)	12.2 (17.2)	0.116	0.919	0.068	0.467
Δ FEV1/FVC (%), mean (SD)	3.1 (7.5)	6.5 (7.0)	3.8 (8.3)	0.17	0.26	0.76	0.39

SD, standard deviation; *SABA*, short-acting beta-agonists; *ACT*, Asthma Control Test; *NP*, nasal polyps; *BEC*, blood eosinophil count; *FEV1*, forced expiratory volume at the end of the first second; *FVC*, forced vital capacity

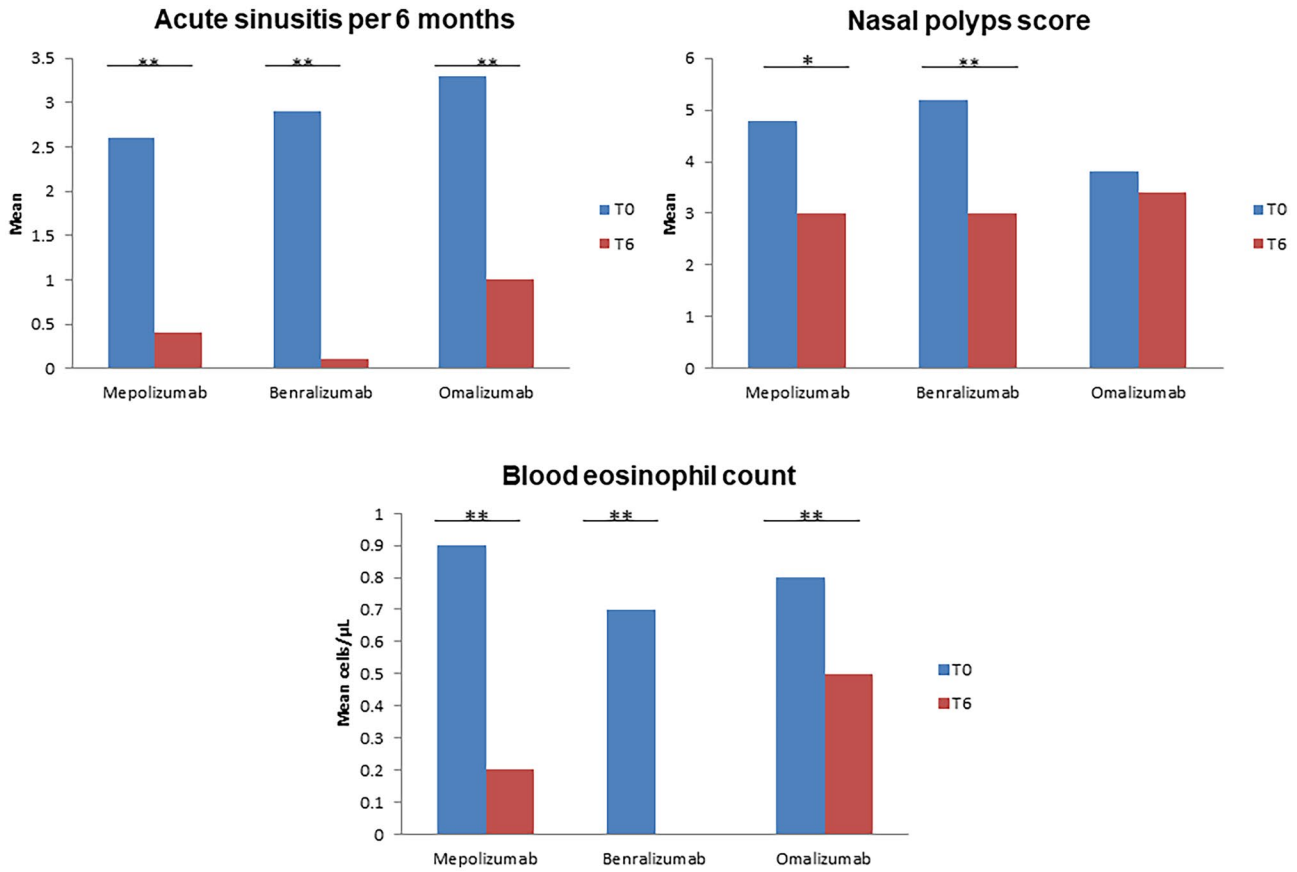

Fig. 2 Nasal polyposis outcomes and blood eosinophil count at baseline (T0) and after 6 months of treatment (T6)

aged ≥ 12 years with ≥ 0.3×10^9 blood eosinophils/L [33]. The present study showed that benralizumab is effective to reduce the rate of exacerbations, to improve the asthma control and the lung function and to deplete blood eosinophils as already described [34], but also to decrease respiratory symptoms (dyspnoea, cough), weekly asthma attacks and SABA use (Table 3, Fig. 1). Similarly, almost all the nasal symptoms have been improved, as well as the NP score with a significant reduction of the number of acute sinusitis per 6 months (Table 3, Fig. 2). A very recent clinical trial demonstrated that benralizumab significantly improved the nasal obstruction, the sense of smell and the NP score after 40 weeks of treatment compared to placebo [35]. The benefits of benralizumab for the association severe eosinophilic asthma- NP have been demonstrated even at 24 weeks of treatment on asthma outcomes (control, exacerbation rate, lung function and related quality of life) and NP with the improvement of the SNOT-22 score [34, 36]. Regarding the association SAA-NP, another small study showed comparable findings with ours for the effectiveness of benralizumab on the nasal symptoms, the NP endoscopic score and BEC reduction [37].

The originality of this work consists in the study of the effectiveness of three different biological therapies in the SAA associated with NP, a particular form of severe asthma resulting from the overlapping between SAA, an IgE-mediated disease and severe eosinophilic asthma driven probably by the innate lymphoid cell 2 activated by alarmins [38]. It is interesting to highlight several characteristics found in this population (Table 1): adult-onset of asthma, predominance of never-smokers, increased levels of BEC typical for the severe eosinophilic asthma [39, 40], predominance of men, frequent previous NP surgery related more to the NP [35], presence of the familial atopy, symptoms such as sneezing, pruritus and high levels of total serum IgE, specific for the allergic respiratory disease [41]. The allergic profile identified in this study is typical for the Western Europe [4, 28]. In the severe eosinophilic allergic asthma, anti-IgE and anti-IL-5/R antibodies could be administrated [1]. The present study confirmed the effectiveness of all these treatments in SAA. In addition, significant benefits of all these biological therapies have been registered on NP outcomes supporting the concept of 'one airway, one disease' [42, 43]. The effectiveness of omalizumab, mepolizumab and benralizumab

Table 5 Odds ratios of failure of biological therapies on studied parameters after 6 months of treatment

Parameter	Biotherapy	OR (CI95%)	Biotherapy	OR (CI95%)
Pruritus	Mepolizumab	1		
	Benralizumab	0.17 (0.01–1.88)	Mepolizumab-Benralizumab	1
	Omalizumab	**0.01 (0.00–0.11)**	Omalizumab	**0.02 (0.00–0.18)**
Loss of smell	Mepolizumab	1		
	Benralizumab	0.47 (0.69–3.35)	Mepolizumab-Benralizumab	1
	Omalizumab	0.36 (0.07–2.34)	Omalizumab	1.90 (0.22–16.57)
Rhinorrhoea	Mepolizumab	1		
	Benralizumab	0.37 (0.08–1.49)	Mepolizumab-Benralizumab	1
	Omalizumab	0.41 (0.10–1.68)	Omalizumab	1.32 (0.69–3.28)
Sneeze	Mepolizumab	1		
	Benralizumab	0.21 (0.03–1.31)	Mepolizumab-Benralizumab	1
	Omalizumab	**0.09 (0.02–0.54)**	Omalizumab	**0.22 (0.06–0.87)**
Nasal obstruction	Mepolizumab	1		
	Benralizumab	0.37 (0.24–0.70)	Mepolizumab-Benralizumab	1
	Omalizumab	0.30 (0.06–1.51)	Omalizumab	0.47 (0.11–2.02)
Dyspnoea	Mepolizumab	1		
	Benralizumab	0.21 (0.02–2.60)	Mepolizumab-Benralizumab	1
	Omalizumab	0.11 (0.01–1.32)	Omalizumab	0.22 (0.02–2.19)
Cough	Mepolizumab	1		
	Benralizumab	0.40 (0.09–1.71)	Mepolizumab-Benralizumab	1
	Omalizumab	1.01 (0.35–3.28)	Omalizumab	1.52 (0.57–4.06)
Daily attacks	Mepolizumab	1		
	Benralizumab	0.19 (0.02–1.80)	Mepolizumab-Benralizumab	1
	Omalizumab	0.97 (0.27–3.46)	Omalizumab	1.67 (0.52–5.34)
Night attacks	Mepolizumab	1		
	Benralizumab	0.27 (0.027–2.70)	Mepolizumab-Benralizumab	1
	Omalizumab	1.79 (0.48–6.69)	Omalizumab	2.77 (0.84–9.12)
SABA use	Mepolizumab	1		
	Benralizumab	0.17 (0.02–1.56)	Mepolizumab-Benralizumab	1
	Omalizumab	1.40 (0.74–7.50)	Omalizumab	**4.05 (1.41–11.64)**
ACT score	Mepolizumab	1		
	Benralizumab	1.33 (0.08–23.08)	Mepolizumab-Benralizumab	1
	Omalizumab	1.87 (0.18–19.29)	Omalizumab	1.64 (0.26–10.46)
Exacerbations	Mepolizumab	1		
	Benralizumab	**0**	Mepolizumab-Benralizumab	1
	Omalizumab	0.73 (0.15–3.62)	Omalizumab	1.53 (0.33–7.15)
Acute Sinusitis	Mepolizumab	1		
	Benralizumab	**0**	Mepolizumab-Benralizumab	1
	Omalizumab	2.25 (0.23–22.14)	Omalizumab	5 (0.53–46.72)
NP score	Mepolizumab	1		
	Benralizumab	0.30 (0.04–2.20)	Mepolizumab-Benralizumab	1
	Omalizumab	0.88 (0.14–5.57)	Omalizumab	1.55 (0.33–7.36)
Sinus CT scan	Mepolizumab	1		
	Benralizumab	0.51 (0.12–2.12)	Mepolizumab-Benralizumab	1
	Omalizumab	1.37 (0.42–4.47)	Omalizumab	1.87 (0.69–5.05)
FEV1 (%)	Mepolizumab	1		
	Benralizumab	2.25 (0.54–9.34)	Mepolizumab-Benralizumab	1
	Omalizumab	1 (0.33–2.98)	Omalizumab	0.72 (0.28–1.87)
FVC (%)	Mepolizumab	1		
	Benralizumab	2 (0.51–7.80)	Mepolizumab-Benralizumab	1
	Omalizumab	0.61 (0.20–1.80)	Omalizumab	0.45 (0.18–1.17)
FEV1/FVC (%)	Mepolizumab	1		
	Benralizumab	0.97 (0.25–3.73)	Mepolizumab-Benralizumab	1
	Omalizumab	0.56 (0.18–1.80)	Omalizumab	0.57 (0.21–1.56)

Table 5 (continued)

Parameter	Biotherapy	OR (CI95%)	Biotherapy	OR (CI95%)
BEC	Mepolizumab	1		
	Benralizumab	**0.07 (0.01–0.66)**	Mepolizumab-Benralizumab	1
	Omalizumab	**11.73 (2.72–50.56)**	Omalizumab	**25.21 (6.36–99.96)**

NP, nasal polyps; *FEV1*, forced expiratory volume at the end of the first second; *FVC*, forced vital capacity; *CT*, computed tomography; *ACT*, Asthma Control Test; *SABA*, short-acting beta-agonists

in the association SAA-NP was comparable for the most of studied parameters (Tables 2 and 4). However, several differences were found such as a greater benefit on the nasal pruritus and sneezing for the patients receiving omalizumab compared to anti-IL5/R. Conversely, benralizumab showed higher effectiveness in the improvement of the exacerbation rate, the number of episode of acute sinusitis and FEV1 than the others. Mepolizumab and benralizumab were more efficient compared to omalizumab to decrease the NP endoscopic score, SABA use and BEC (Tables 2, 4 and 5). To the best of our knowledge, this is the first study that compared biological therapies face-to-face in the SAA-NP in real-life setting. Currently, there are limited data comparing the effectiveness of biological therapies in severe asthma and NP. A small prospective Italian study showed comparable effectiveness of these three biological therapies in severe asthma patients with NP with similar improvement of the SNOT-22 and endoscopic scores at 52 weeks of treatment [44]. Limitations of our study include retrospective design, limited number of patients, unequal distribution in the three groups related to the availability of these products in both countries and 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 biological therapy is more efficient at a specific outcome.

In summary, this study showed comparable effectiveness of all three biological therapies in SAA associated with NP by improving asthma and nasal disease outcomes. Some differences in treatment effects were found with greater benefits on asthma and NP outcomes in patients treated by benralizumab while the patients treated by omalizumab have more chances for an improvement of their nasal allergic symptoms. Larger comparative studies are needed to verify these preliminary results.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s12016-022-08938-w.

Declarations

Conflict of Interest Iulia Ioan, Rodrigo Romero-Fernandez, Thi-cam-tu Hoang and Diana Carolina Ochoa-Gutierrez have no conflicts of interest. Angelica Tiotiu reports speaker and consulting fees from ALK, AstraZeneca, GSK, Novartis and Sanofi outside the submitted work. Paula Méndez-Brea Paula reports personal fees from ALK, Allergy Therapeutics, Chiesi, GSK and Stallergenes outside the submitted work. Jean Philippe Oster reports speaker and consulting fees from AstraZeneca, GSK, Novartis and Sanofi outside the submitted work. Pauline Roux reports speaker and consulting fees from AstraZeneca, Chiesi, GSK and Novartis outside the submitted work. Philippe Bonniaud reports speaker and consulting fees from AstraZeneca, Chiesi, GSK, Novartis and Sanofi outside the submitted work. Frederic de Blay reports speaker and consulting fees from ALK, AstraZeneca, Chiesi, GSK, Novartis and Sanofi outside the submitted work. Francisco-Javier Gonzalez-Barcala has received speaker fees, consulting fees or research grants from ALK, AstraZeneca, Bial, Boehringer-Ingelheim, Chiesi, Gebro Pharma, GSK, Laboratorios Esteve, Menarini, Mundipharma, Novartis, Rovi, Roxall, Sanofi, Stallergenes and Teva.

References

1. GINA Difficult-to-treat & severe asthma in adolescent and adult patients. Diagnosis and management; 2021. Available from: https://ginasthma.org/wp-content/uploads/2021/08/SA-Pocket-guide-v3.0-SCREEN-WMS.pdf. [cited 2021 Nov 16]
2. Humbert M, Bousquet J, Bachert C, Palomares O, Pfister P, Kottakis I et al (2019) IgE-mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. J Allergy Clin Immunol Pract 7:1418–1429
3. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J et al (2015) Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. Eur Respir J 46:1308–1321
4. Pretolani M, Soussan D, Poirier I, Thabut G, Aubier M, COBRA Study Group et al (2017) Clinical and biological characteristics of the French COBRA cohort of adult subjects with asthma. Eur Respir J 50:1700019. https://doi.org/10.1183/13993003.00019-2017
5. Wang E, Wechsler ME, Tran TN, Heaney LG, Jones RC, Menzies-Gow AN et al (2020) Characterization of severe asthma worldwide: data from the international severe asthma registry. Chest 157:790–804
6. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S et al (2020) European position paper on rhinosinusitis and nasal polyps 2020. Rhinology 58(Suppl S29):1–464
7. Bilodeau L, Boulay M-E, Prince P, Boisvert P, Boulet L-P (2010) Comparative clinical and airway inflammatory features of asthmatics with or without polyps. Rhinology 48:420–425
8. Bhattacharyya N, Villeneuve S, Joish VN, Amand C, Mannent L, Amin N et al (2019) Cost burden and resource utilization in patients with chronic rhinosinusitis and nasal polyps. Laryngoscope 129:1969–1975
9. Bagnasco D, Brussino L, Bonavia M, Calzolari E, Caminati M, Caruso C et al (2020) Efficacy of Benralizumab in severe asthma in real life and focus on nasal polyposis. Respir Med 171:106080. https://doi.org/10.1016/j.rmed.2020.106080

10. Blakey JD, Price DB, Pizzichini E, Popov TA, Dimitrov BD, Postma DS et al (2017) Identifying risk of future asthma attacks using UK medical record data: a respiratory effectiveness group initiative. J Allergy Clin Immunol Pract 5:1015–1024
11. Mümmler C, Dünzelmann K, Kneidinger N, Barnikel M, Munker D, Gröger M et al (2021) Real-life effectiveness of biological therapies on symptoms in severe asthma with comorbid CRSwNP. Clin Transl Allergy 11:e12049. https://doi.org/10.1002/clt2.12049
12. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SE et al (2019) Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. Lancet 394:1638–1650
13. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE et al (2020) Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. J Allergy Clin Immunol 146:595–605
14. Han JK, Bachert C, Fokkens W, Desrosiers M, Wagenmann M, Lee SE et al (2021) Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Respir Med 9:1141–1153
15. Heinzerling L, Mari A, Bergmann K-C, Bresciani M, Burbach G, Darsow U et al (2013) The skin prick test - European standards. Clin Transl Allergy 3:3. https://doi.org/10.1186/2045-7022-3-3
16. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A et al (2005) Standardisation of spirometry. Eur Respir J 26:319–338
17. GINA Main Report 2021.Available from: https://ginasthma.org/wp-content/uploads/2021/05/GINA-Main-Report-2021-V2-WMS.pdf. [cited 2021 Nov 21]
18. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W et al (2013) Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol 131:110-116.e1
19. Abraham I, Alhossan A, Lee CS, Kutbi H, MacDonald K (2016) 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: systematic review. Allergy 71:593–610
20. Alhossan A, Lee CS, MacDonald K, Abraham I (2017) 'Real-life' effectiveness studies of omalizumab in adult patients with severe allergic asthma: meta-analysis. J Allergy Clin Immunol Pract 5:1362-1370.e2
21. Damask C, Chen M, Holweg CTJ, Yoo B, Millette LA, Franzese C (2022) Defining the efficacy of omalizumab in nasal polyposis: a POLYP 1 and POLYP 2 subgroup analysis. Am J Rhinol Allergy 36:135–141
22. Novartis. Xolair (omalizumab) label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/103976s5238lbl.pdf#page=36. [cited 2021 Dec 21]
23. Agache I, Song Y, Alonso-Coello P, Vogel Y, Rocha C, Solà I et al (2021) Efficacy and safety of treatment with biologicals for severe chronic rhinosinusitis with nasal polyps: A systematic review for the EAACI guidelines. Allergy 76:2337–2353
24. Tsabouri S, Ntritsos G, Koskeridis F, Evangelou E, Olsson P, Kostikas K (2021) Omalizumab for the treatment of allergic rhinitis: a systematic review and meta-analysis. Rhinology 59:501–510
25. Bidder T, Sahota J, Rennie C, Lund VJ, Robinson DS, Kariyawasam HH (2018) Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together-a real life study. Rhinology 56:42–45
26. Heffler E, Saccheri F, Bartezaghi M, Canonica GW (2020) Effectiveness of omalizumab in patients with severe allergic asthma with and without chronic rhinosinusitis with nasal polyps: a PROXIMA study post hoc analysis. Clin Transl Allergy 10:25. https://doi.org/10.1186/s13601-020-00330-1
27. Ruiz-Hornillos J, Rodríguez Jiménez B, Feliu Vila A, Moreno Fernández A, Hernández García MJ, Domínguez-Ortega J et al (2020) Omalizumab as a therapeutic option for nasal polyposis in moderate-to-severe persistent allergic asthma: evidence from a prospective study in a real-world setting. J Investig Allergol Clin Immunol 30:470–472
28. Tiotiu A, Oster JP, Roux PR, Nguyen Thi PL, Peiffer G, Bonniaud P et al (2020) Effectiveness of omalizumab in severe allergic asthma and nasal polyposis: a real-life study. J Investig Allergol Clin Immunol 30:49–57
29. GlaxoSmithKline LLC. Nucala (mepolizumab) label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/761122s006,125526s018lbl.pdf. [cited 2021 Dec 26]
30. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A et al (2014) Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 371:1198–1207
31. Khatri S, Moore W, Gibson PG, Leigh R, Bourdin A, Maspero J et al (2019) Assessment of the long-term safety of mepolizumab and durability of clinical response in patients with severe eosinophilic asthma. J Allergy Clin Immunol 143:1742-1751.e7
32. Howarth P, Chupp G, Nelsen LM, Bradford ES, Bratton DJ, Smith SG et al (2020) Severe eosinophilic asthma with nasal polyposis: a phenotype for improved sinonasal and asthma outcomes with mepolizumab therapy. J Allergy Clin Immunol 145:1713–1715
33. AstraZeneca. Fasenra (benralizumab) label. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761070s005lbl.pdf. [cited 2021 Dec 28]
34. Harrison TW, Chanez P, Menzella F, Canonica GW, Louis R, Cosio BG et al (2021) Onset of effect and impact on health-related quality of life, exacerbation rate, lung function, and nasal polyposis symptoms for patients with severe eosinophilic asthma treated with benralizumab (ANDHI): a randomised, controlled, phase 3b trial. Lancet Respir Med 9:260–274
35. Bachert C, Han JK, Desrosiers MY, Gevaert P, Heffler E, Hopkins C et al (2021) Efficacy and safety of benralizumab in chronic rhinosinusitis with nasal polyps: a randomized, placebo-controlled trial. J Allergy Clin Immunol S0091–6749(21):01459–01467. https://doi.org/10.1016/j.jaci.2021.08.030
36. Canonica GW, Harrison TW, Chanez P, Menzella F, Louis R, Cosio BG et al (2022) Benralizumab improves symptoms of patients with severe, eosinophilic asthma with a diagnosis of nasal polyposis. Allergy 77:150–161
37. Lombardo N, Pelaia C, Ciriolo M, Della Corte M, Piazzetta G, Lobello N et al (2020) Real-life effects of benralizumab on allergic chronic rhinosinusitis and nasal polyposis associated with severe asthma. Int J Immunopathol Pharmacol 34:2058738420950851. https://doi.org/10.1177/2058738420950851
38. Wenzel SE (2021) Severe adult asthmas: integrating clinical features, biology, and therapeutics to improve outcomes. Am J Respir Crit Care Med 203:809–821
39. Taillé C, Chanez P, Devouassoux G, Didier A, Pison C, Garcia G et al (2020) Mepolizumab in a population with severe eosinophilic asthma and corticosteroid dependence: results from a French early access programme. Eur Respir J 55:1902345. https://doi.org/10.1183/13993003.02345-2019
40. Kavanagh JE, Hearn AP, Dhariwal J, d'Ancona G, Douiri A, Roxas C et al (2021) Real-world effectiveness of benralizumab in severe eosinophilic asthma. Chest 159:496–506
41. Humbert M, Boulet LP, Niven RM, Panahloo Z, Blogg M, Ayre G (2009) Omalizumab therapy: patients who achieve greatest benefit for their asthma experience greatest benefit for rhinitis. Allergy 64:81–84
42. Samitas K, Carter A, Kariyawasam HH, Xanthou G (2018) Upper and lower airway remodelling mechanisms in asthma, allergic rhinitis and chronic rhinosinusitis: the one airway concept revisited. Allergy 73:993–1002
43. Tiotiu A, Novakova P, Baiardini I, Bikov A, Chong-Neto H, de-Sousa JC et al (2021) Manifesto on united airways diseases (UAD): an Interasma (global asthma association - GAA) document. J Asthma 1–16. https://doi.org/10.1080/02770903.2021.1879130

44. Bandi F, Gallo S, Preti A, Mozzanica F, Visca D, Marelli M et al (2020) Effects of biological therapies on chronic rhinosinusitis in severe asthmatic patients. Acta Otorhinolaryngol Ital 40:435–443

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Authors and Affiliations

Angelica Tiotiu[1,2] · Paula Mendez-Brea[3] · Iulia Ioan[2,4] · Rodrigo Romero-Fernandez[5] · Jean Philippe Oster[6] · Thi-cam-tu Hoang[6] · Pauline Roux[7] · Diana Carolina Ochoa-Gutierrez[8] · Philippe Bonniaud[9,10,11] · Frederic de Blay[8,12] · Francisco-Javier Gonzalez-Barcala[13,14,15]

Paula Mendez-Brea
paula.mendez.brea@sergas.es

Iulia Ioan
ic.ioan@chru-nancy.fr

Rodrigo Romero-Fernandez
rodrigo.romero.fernandez@sergas.es

Jean Philippe Oster
jeanphilippe.oster@ch-colmar.fr

Thi-cam-tu Hoang
thicamtu.hoang@gmail.com

Pauline Roux
pmroux@chu-besancon.fr

Diana Carolina Ochoa-Gutierrez
diana-carolina.ochoa-gutierrez@chru-strasbourg.fr

Philippe Bonniaud
philippe.bonniaud@chu-dijon.fr

Frederic de Blay
Frederic.DEBLAY@chru-strasbourg.fr

Francisco-Javier Gonzalez-Barcala
francisco.javier.gonzalez.barcala@sergas.es

[1] Department of Pulmonology, University Hospital of Nancy, 9 Rue du Morvan, 54500 Vandoeuvre-Les-Nancy, Nancy, France

[2] Development, Adaptation and Disadvantage, Cardiorespiratory Regulations and Motor Control (EA 3450 DevAH), University of Lorraine, Nancy, France

[3] Department of Allergy, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain

[4] Lung Function Testing Lab, Children's University Hospital of Nancy, Nancy, France

[5] Department of Medicine, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain

[6] Department of Pulmonology, Hospital of Colmar, Colmar, France

[7] Department of Pulmonology, University Hospital of Besançon, Besançon, France

[8] Department of Pulmonology-Allergology, University Hospital of Strasbourg, Strasbourg, France

[9] Department of Pulmonary Medicine and Intensive Care Unit, University Hospital of Dijon, Dijon, France

[10] LNC UMR866, LipSTIC LabEx Team, Inserm, Dijon, France

[11] Bourgogne Franche-Comté University, Dijon, France

[12] University of Strasbourg, Strasbourg, France

[13] Department of Respiratory Medicine, University Hospital of Santiago de Compostela, Santiago de Compostela, Spain

[14] Spanish Biomedical Research Networking Centre-CIBERES, Santiago de Compostela, Spain

[15] Health Research Institute of Santiago de Compostela (FIDIS), Santiago de Compostela, Spain