ORIGINAL ARTICLE

Improvement in Olfaction in Patients With CRSwNP and Severe Asthma Taking Anti-IgE and Anti–IL-5 Biologics: A Real-Life Study

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP), which is characterized by partial loss of smell (hyposmia) or total loss of smell (anosmia), is commonly associated with asthma and/or nonsteroidal anti-inflammatory drug–exacerbated respiratory disease (N-ERD). CRSwNP worsens disease severity and quality of life.
Objectives: The objective of this real-world study was to determine whether biological treatments prescribed for severe asthma can improve olfaction in patients with CRSwNP. A further objective was to compare the improvement in in olfaction in N-ERD and non–N-ERD subgroups.
Methods: We performed a multicenter, noninterventional, retrospective, observational study of 206 patients with severe asthma and CRSwNP undergoing biological treatment (omalizumab, mepolizumab, benralizumab, or reslizumab).
Results: Olfaction improved after treatment with all 4 monoclonal antibodies (omalizumab [35.8%], mepolizumab [35.4%], reslizumab [35.7%], and benralizumab [39.1%]), with no differences between the groups. Olfaction was more likely to improve in patients with atopy, more frequent use of short-course systemic corticosteroids, and larger polyp size. The proportion of patients whose olfaction improved was similar between the N-ERD (37%) and non–N-ERD (35.7%) groups.
Conclusions: This is the first real-world study to compare improvement in olfaction among patients undergoing long-term treatment with omalizumab, mepolizumab, reslizumab, or benralizumab for severe asthma and associated CRSwNP. Approximately 4 out of 10 patients reported a subjective improvement in olfaction (with nonsignificant differences between biologic drugs). No differences were found for improved olfaction between the N-ERD and non–N-ERD groups.

Key words: Benralizumab. CRSwNP. Mepolizumab. Nasal polyps. Olfaction. Omalizumab. Reslizumab. Smell.

Resumen

Introducción: La rinosinusitis crónica con poliposis nasal (PN), caracterizada por la pérdida parcial o completa del olfato (hiposmia o anosmia, respectivamente), se asocia frecuentemente a asma y a enfermedad respiratoria exacerbada por ácido acetilsalicílico (EREA), lo cual implica una mayor gravedad y un deterioro adicional de la calidad de vida del paciente.
Objetivos: El objetivo principal de este estudio fue determinar, en condiciones de vida real, si los tratamientos biológicos prescritos para asma grave mejoraban el olfato en aquellos pacientes que asociaban PN. Como objetivo secundario, se comparó la mejoría del olfato entre los subgrupos EREA y no EREA.
Métodos: Se llevó a cabo un estudio multicéntrico, observacional, retrospectivo, que incluyó 206 pacientes con PN y asma grave en tratamiento con algún biológico (omalizumab, mepolizumab, benralizumab oreslizumab).
Resultados: Se encontró mejoría del olfato con todos los biológicos: omalizumab (35,8%), mepolizumab (35,4%), reslizumab (35,7%) y benralizumab (39,1%), sin diferencias estadísticamente significativas entre ellos. Los pacientes con atopia, mayor uso de corticoides sistémicos y mayor tamaño de PN inicial, presentaron mayor mejoría. La proporción de pacientes que presentaron mejoría en el olfato fue similar entre el grupo EREA (37%) y no EREA (35,7%).
Conclusiones: Se trata del primer estudio que compara, en condiciones de vida real, la mejoría del olfato en pacientes en tratamiento con omalizumab, mepolizumab, reslizumab o benralizumab indicados por asma grave que asociaban PN. Aproximadamente, 4 de cada 10 pacientes refirió mejoría subjetiva en el olfato (sin diferencias estadísticamente significativas entre los distintos biológicos). No se encontraron diferencias entre el grupo EREA y no EREA.

Palabras clave: Benralizumab. RSCcPN. Mepolizumab. Pólipos nasales. Olfato. Omalizumab. Reslizumab. Olor.

Introduction

Chronic rhinosinusitis (CRS) can be divided into 2 main phenotypes: with nasal polyps (CRSwNP) and without nasal polyps. CRSwNP is commonly associated with asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) [1,2]. This multimorbidity worsens the severity of CRSwNP and quality of life and increases treatment-related costs [3,4]. The main sinonasal symptoms of CRSwNP are nasal congestion/blockage, facial pain/pressure, nasal discharge/postnasal drip, and partial loss of smell (hyposmia) or total loss of smell (anosmia), which have a negative impact on patient quality of life [5].

Approximately 80% of cases are driven by type 2 inflammation, which is characterized by upregulation of interleukin (IL) 4, IL-5, and IL-13, with increased immunoglobulin E (IgE) antibodies in tissue and plasma [6,7]. This pattern is strongly associated with asthma and loss of smell [7] and contrasts with the noneosinophilic inflammatory endotype.

Loss of smell is a quantitative dysfunction of olfaction, as measured by hyposmia and anosmia values. Alone, this symptom is a potent predictor of CRS [8,9] and has been identified as an independent risk factor for death among older adults [10]. Additionally, an impaired sense of smell is related to low quality of life [11], with higher rates of depression [12] and disease severity [13]. Loss of smell is more frequent in the type 2 endotype of CRSwNP and is associated with respiratory diseases such as asthma [1,7,14,15], bronchiectasis [16], and N-ERD [2,17].

Given the type 2–driven inflammation in most cases of CRSwNP, specific monoclonal antibodies have been developed, including the anti-IgE agent omalizumab, the anti–IL-5 agents mepolizumab, reslizumab, and benralizumab, and the anti–IL-4/IL-13 agent dupilumab[3-4]. Although some indirect comparative studies have been published [18-20], no head-to-head comparisons between biologics have been carried out in CRSwNP.

The main objectives of this real-world study were to determine whether monoclonal antibodies prescribed for the treatment of severe asthma can improve olfaction in patients with CRSwNP and to establish differences between monoclonal antibodies based on their respective targets (IgE, IL-5, and IL-4/IL-13). A further objective was to compare the N-ERD subgroup, usually the most severe pheno-endotype of CRSwNP, with non–N-ERD patients and to arbitrarily compare patients with different blood eosinophil counts (BECs).

Methods

Study Population

We performed a multicenter, noninterventional, retrospective, observational, real-life study in the allergology and pulmonology departments of 9 hospitals belonging to the Spanish Asthma Network [21,22]. The study population comprised 545 patients aged ≥18 years diagnosed with severe asthma and who were undergoing biological treatment (omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) [23] in accordance with the criteria of the Global Initiative for Asthma [24] for a minimum of 1 year. For this study, only patients with CRSwNP (diagnosed based on the presence of sinonasal symptoms and nasal endoscopy and/or CT findings) [3] were selected. The dupilumab subgroup was excluded from the analysis owing to its small size (n=4).

Study Design and Ethics

We performed a retrospective review of electronic medical records to collect patient data such as demographic characteristics, atopy (defined as positive specific IgE in serum or at least 1 positive skin prick test result for common aeroallergens), history of N-ERD, monoclonal antibodies used, treatment duration, asthma outcomes (years since diagnosis, number of exacerbations in the previous year,

Asthma Control Test [ACT] score, forced expiratory volume in 1 second [FEV_1], fractional exhaled nitric oxide [FeNO]), and blood eosinophil count (BEC).Onset of CRSwNP, use of nasal and systemic corticosteroids (SCS), and number of endonasal endoscopic surgery (EES) procedures were also recorded before and after biologic treatment. Approval was obtained from the institutional ethics committees of all the participating hospitals.

Olfaction was evaluated subjectively at a minimum of 2 time points, ie, before biologic treatment and during biologic treatment. Patients answered yes or no to a question on the degree of loss of smell: none (normosmia), partial (hyposmia), or total (anosmia). As data on olfaction during biological treatment were registered during the SARS-CoV-2 pandemic (SARS-CoV-2 can cause hyposmia/anosmia), data on olfaction from before infection were used to avoid possible bias. On the other hand, the presence of CRSwNP/eosinophilic CRS protects against the loss of smell induced by COVID-19 owing to downregulation of ACE2 and *TMPRSS2* in the olfactory neuroepithelium of CRSwNP patients [25].

Using nasal endoscopy, polyp size was scored by an ENT specialist and/or allergist on a scale of 0-4 per side according to the criteria of Meltzer [26].The median (IQR) number was obtained for the left and right nostril.

Outcomes

We evaluated changes in olfaction before and after biological treatment by means of 3 possible values: partial improvement (change from anosmia to hyposmia), total improvement (change from anosmia or hyposmia to normosmia), and no improvement (no improvement or deterioration). We also analyzed these data to determine whether there were any differences between these 3 categories depending on the biologic treatment used. We then performed a subanalysis to search for possible differences in improvement in olfaction between the N-ERD and non–N-ERD subgroups by arbitrarily comparing patients with different BEC levels, ie, <500 vs ≥500/μL and <300 vs ≥300/μL (cut-off point of previous studies with CRSwNP and biologics).

Statistical Analysis

Details on the statistical analysis are provided in the Supplementary Material.

Results

Demographic Characteristics

From the initial cohort of 545 patients with severe asthma treated with a monoclonal antibody, 225 (41.3%) had CRSwNP. Fifteen patients were excluded owing to a lack of information on olfaction. The dupilumab subgroup (n=4) was also excluded from the analysis owing to its small sample size (Supplementary figure 1). As a result, the total sample included 206 patients (age range, 56 [13] years; 56.8% female) (Supplementary table 1).

Of the 206 patients included, 81 (39.3%) were treated with omalizumab, 65 (31.6%) with mepolizumab, 14 (6.8%) with reslizumab, and 46 (22.3%) with benralizumab. The mean time of treatment varied from 1.9 to 5.8 years (Supplementary table 1). All groups were homogeneous in terms of the variables studied, except for presence of atopy, as the mepolizumab group contained significantly fewer patients with atopy than the omalizumab and reslizumab groups (P=.02). Another difference concerned the time of treatment (P=.0001) between almost all biologic groups except for those treated with mepolizumab and reslizumab. An association with N-ERD was detected in 92 patients (44.7%), most of whom were treated with omalizumab (41/92).

The mean time since onset of asthma was 21 (13) years. Lung function (FEV_1), number of asthma exacerbations per year, and ACT score improved in all groups.

At baseline, the mean BEC of asthmatics with CRswNP was 541 (369)/μL. Patients with mepolizumab had higher counts than those receiving omalizumab (P=.005) and benralizumab (P=.04). After biological treatment, a marked decrease in BEC was observed for the anti–IL-5 biologics compared with omalizumab (P<.0001).

The mean time since onset of CRSwNP was 14.4 (10.2) years. At baseline, the overall sample was homogeneous in terms of nasal polyp size, with a median score of 2 out of 4 according to Meltzer et al [26]. Other common features included use of short courses of SCS (1.7 [2] cycles per year) and a median of 1 EES procedure (0-2). During treatment with monoclonal antibodies, there was a significant reduction in polyp size (overall, P≤.0001), use of SCS (overall, P<.0001), and need for EES in the groups receiving omalizumab, mepolizumab, and benralizumab (overall, P<.0001). A statistically significant decrease in the number of EES procedures was observed in patients taking reslizumab (P=.0039). A reduction was observed in polyp size (P=.9041) and SCS use (P=.0625) from baseline to completion of therapy with reslizumab; however, these changes did not reach statistical significance (Table).

Regarding olfaction, pretreatment presence of hyposmia and normosmia was homogenous between groups of biologics, although significant differences were observed for anosmia. The omalizumab and mepolizumab groups included significantly more patients with anosmia than the group treated with benralizumab (P=.03 and P=.04, respectively), both before and after biologic treatment. A comparison of olfaction between baseline and therapy with biologics showed an increase in patients with normosmia that proved to be statistically significant when the entire sample was analyzed (P=.0004); however, when biologic groups were compared, only the increase in normosmia in the omalizumab group proved to be statistically significant (P=.041). The significant decrease in the percentage of patients with anosmia from baseline to therapy with biologics was noteworthy (P<.0001) throughout the sample. This decrease was also statistically significant in all groups except the reslizumab group (Supplementary figure 2).

Improvement in Olfaction

A total or partial improvement in loss of smell was found after treatment with monoclonal antibodies (omalizumab [35.8%], mepolizumab [35.4%], reslizumab [35.7%], and benralizumab [39.1%]), with no differences between the groups (Figure). Approximately 61% to 64% of patients experienced

Table. Data on Asthma, Blood Eosinophils Count, CRSwNP and Smell Before and During Biologic Treatment

	Total			Omalizumab			Mepolizumab			Reslizumab			Benralizumab		
	Pre	Post	*P* Value	Pre	Post	*P* Value	Pre	Post	*P* Value	Pre	Post	*P* Value	Pre	Post	*P* Value
Mean (SD) FEV_1, %	71.2 (24.6)	74.8 (30.5)	<.0001	74.0 (21.4)	86.6 (21.1)	<.0001	63.0 (22.8)	78.3 (19.5)	.0003	58.6 (31.2)	80.2 (20.2)	0.0140	73.0 (18.2)	79.8 (19.4)	<.0001
Mean (SD) FeNO, ppb	65.0 (53.1)	49.2 (45.7)	.0008	58.2 (38.6)	40.4 (38.8)	<.0001	72.3 (65.7)	47.8 (37.3)	.0212	59.5 (38.8)	75.4 (52.6)	0.3105	63.3 (53.7)	58.5 (61.8)	.6444
Mean ACT score	16.1 (5.8)	22.3 (5.4)	<.0001	17.2 (0.15)	21.7 (3.3)	<.0001	16.1 (4.5)	22.2 (2.8)	<.0001	12.4 (4.7)	24.2 (1.4)	0.0002	16.4 (6.6)	22.2 (4.3)	<.0001
Mean (SD) asthma exacerbations per year	3.1 (2.4)	0.5 (1)	.0007	3.3 (2.7)	0.5 (0.7)	<.0001	4.2 (2.1)	0.7 (0.9)	<.0001	3.71 (1.8)	0.1 (0.4)	<0.0001	3.1 (2.1)	0.5 (1.4)	<.0001
Mean BEC, cells/µL	541 (369)	186 (239)	<.0001	477 (315)	368 (274)	.0045	652 (410)	92 (84)	<.0001	529 (355)	63 (42)	0.0015	509 (379)	6 (20)	<.0001
Normosmia, No. (%)	29 (14.1)	62 (30.1)	.0004	7 (8.6)	22 (27.2)	.0041	11 (16.9)	19 (29.2)	.1642	2 (14.0)	4 (28.57)	0.6451	9 (19.6)	17 (37)	.1695
Hyposmia, No. (%)	70 (33.3)	88 (42.7)	.0678	26 (32.1)	29 (35.8)	.7400	17 (26.3)	27 (41.5)	.0953	5 (35.7)	8 (57.14)	0.4485	22 (47.8)	24 (52.2)	.6766
Anosmia, No. (%)	107 (51.9)	56 (25.7)	<.0001	48 (59.2)	30 (37.1)	.0075	37 (56.9)	19 (29.2)	.0026	7 (50.2)	2 (14.3)	0.1055	15 (32.6)	5 (11.6)	.0229
Median grade of polyposis (0-4)	2 (0-4)	1 (0-4)	<.0001	2 (0-4)	1 (0-3)	<.0001	2 (0-4)	1 (0-4)	.0013	2 (0-4)	2 (0-3)	0.9041	2 (0-4)	1 (0-4)	<.0001
Use of intranasal corticosteroids, No. (%)	198 (91.9)	198 (96.1)	.0126	80 (98.8)	74 (91.4)	.0698	59 (90.8)	54 (83)	.2981	12 (85.7)	12 (85.7)	0.5892	43 (93.5)	38 (82.6)	.7813
Mean (SD) systemic corticosteroids, short cycles per year	1.7 (2)	0.4 (0.8)	<.0001	2 (2.5)	0.4 (0.8)	<.0001	2 (2.2)	0.5 (0.8)	<.0001	1.4 (2.2)	0.1 (0.3)	0.0625	1 (1)	0.3 (0.8)	<.0001
Median (IQR) no. of EES per year	1 (0-2)	0 (0-2)	<.0001	1 (0-2)	0 (0-2)	<.0001	1 (0-2)	0 (0-1)	<.0001	1 (0-2)	0	0.0039	1 (0-2)	0 (0-1)	<.0001

Abbreviations: ACT, Asthma Control Test; BEC, blood eosinophil count; CRSwNP, chronic rhinosinusitis with nasal polyps; EES, endoscopic endonasal surgery; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 second; IQR, interquartile range; Post, during biologic treatment; Pre, before biologic treatment.

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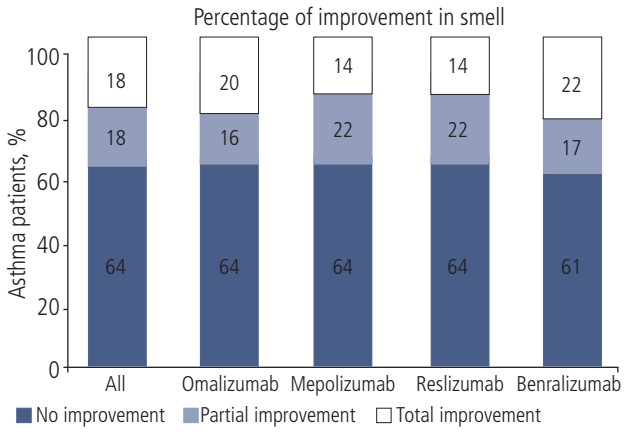

Figure. Changes in olfaction. No improvement, partial improvement (change from anosmia to hyposmia), and total improvement (from anosmia or hyposmia to normosmia). No statistically significant differences were found between the normosmia, hyposmia, and anosmia groups for any of the biologics.

no improvement, and no statistically significant differences were found between biologic treatments.

Partial improvement (from anosmia to hyposmia) was observed in those who received omalizumab (16%), mepolizumab (22%), reslizumab (22%), and benralizumab (17%), with no differences between the groups. Total improvement was reached in patients receiving omalizumab (20%), mepolizumab (14%), reslizumab (14%), and benralizumab (22%), with no differences between the groups.

An analysis of patients whose olfaction improved and did not improve after therapy revealed certain pretreatment differences in sociodemographic and clinical variables (Supplementary table 2). Olfaction was more likely to improve in patients with atopy, increased use of short SCS cycles, and greater nasal polyp size. There were no differences between the drugs in terms of their efficacy (improvement vs no improvement) after adjustment for duration of biologic therapy and frequency of anosmia before biologic therapy.

A striking difference in mean BEC before treatment was observed between the groups experiencing total or partial improvement, as those patients who experienced total improvement had a significantly higher BEC (P=.05), although this was similar to the BEC of the no improvement group (P=.52). Moreover, the partial improvement group needed more EES procedures (P=.01) than the total improvement group, although the number was similar to that of the no improvement group (P=.13) (Supplementary table 2).

After biologic treatment, asthma exacerbations were less frequent in the total improvement than in the no improvement group (P=.008), while intranasal corticosteroids (INCS) were more commonly prescribed in the partial improvement group than in the total improvement group (P=.02) and the no improvement group (P=.008) (Supplementary table 2).

N-ERD Analysis

The N-ERD and non–N-ERD groups were comparable in terms of demographics, onset of asthma, duration of biologic treatment, lung function, FeNO, control of asthma, asthma exacerbations, and mean BEC before and after biologic therapy (Supplementary table 3).

At baseline, N-ERD patients were more likely to develop CRSwNP, had greater smell impairment (fewer patients with normosmia), and had a higher number of EES than non–N-ERD patients. No differences were found in nasal polyp size, use of SCS, or INCS.

After biologic treatment, the percentage of patients with normosmia was higher in the non–N-ERD group. The proportion of patients whose olfaction improved was similar in N-ERD patients (37.0%) and non–N-ERD patients (35.7%). Similar results were also found between the groups for total improvement (17.4% with N-ERD vs 18.3% with non–N-ERD) and partial improvement (19.6% with N-ERD vs 17.4% with non–N-ERD).

Blood Eosinophil Count Analysis

The comparison of total improvement, partial improvement, and no improvement between patients with a high BEC and patients with a low BEC (<500 vs ≥500/μL) revealed no statistically significant differences. Similarly, no statistically significant differences were found between the different biologic groups. Using the BEC cut-off (<300 vs ≥300/μL), no differences were found in total, partial, or no improvement in olfaction between the BEC groups.

Discussion

The demographic characteristics of this severe asthma cohort resemble those reported elsewhere [27,28]. As we can observe, our sample meets the clinical characteristics of the T2 endotype as described by Stevens et al [7]. The differences found in mean duration of treatment with biologics between almost all the groups, except between mepolizumab and reslizumab, are probably due to variations in the commercial availability of each drug. Although patients with atopy are less widely represented in the group that received mepolizumab, based on the results for improvement in smell, this fact does not seem to be relevant.

In our sample (51.9% of patients with anosmia and 33.3% of those with hyposmia), olfaction improved in 35% to 39% of patients. The distribution of improvement by drug was as follows: omalizumab, 35.8%; mepolizumab, 35.4%; reslizumab, 35.7%; and benralizumab, 39.1%. No differences were recorded between monoclonal antibodies for total or partial improvement, regardless of the duration of treatment, or for the percentage of patients with initial anosmia. Olfaction improved more frequently in patients with atopy, those more frequently using short SCS cycles, and those with greater nasal polyp size at baseline. INCS were more frequently prescribed in the partial improvement group.

As expected, respiratory function, airway inflammation, and asthma control were significantly improved by treatment with monoclonal antibodies in all groups, except for reslizumab, where an increase in FeNO was observed.

BEC decreased in all cases after biological treatment. This reduction was more marked with mepolizumab, benralizumab, and reslizumab, as expected, owing to their mechanisms of

action. As omalizumab does not target eosinophil function or programmed apoptosis in eosinophils, BEC does not develop as intensely as with anti–IL-5 treatments [29-31].

The N-ERD and non–N-ERD groups were comparable in terms of demographic characteristics, asthma profile, and mean BEC. N-ERD had a negative impact on smell (fewer patients with normosmia) and a higher need for EES, which is consistent with the poor response to INCS and SCS described in the literature [2-4]. The improvement in olfaction was similar in N-ERD (37.0%) and non–N-ERD patients (35.7%), with no differences for partial or total improvement, in contrast with the available evidence on outcomes regarding improvement in smell with conventional treatments.

In patients with CRSwNP, circulating eosinophils enter a preactivation state that precedes extravasation and migration to nasal polyps [32]. Therefore, blood eosinophilia has been correlated with eosinophilic inflammation endotype [33] and is used to diagnose eosinophilic CRS. Tokunaga et al [34] concluded that BEC was associated with recurrence of disease and need for further surgical intervention but not with improvement in smell. In our study, no differences related to improved olfaction were associated with blood eosinophilia, irrespective of whether the cut-off was 300 or 500/μL.

This long-term (mean, 3.7 [2.6] years), head-to-head, real-world study shows that olfaction improved in 36.1% of patients with severe asthma and associated CRSwNP. The improvement was similar for both N-ERD and non–N-ERD patients (35.7% vs 37.0%).

To date, the only biologic treatments approved by the European Medicines Agency for use in adults with severe CRSwNP who do not respond to first-line treatment are dupilumab, omalizumab, and mepolizumab. Dupilumab has proven highly effective for improving olfaction, as shown by the University of Pennsylvania Smell Identification Test (UPSIT), and for improving quality of life, as evaluated using the Sino-Nasal Outcome Test (SNOT-22) [35]. In 2 randomized placebo-controlled phase 3 trials, dupilumab significantly improved objective measures (nasal polyp score, total symptom score, and severity of rhinosinusitis according to a visual analog scale [VAS]) and patient-reported symptoms to a greater extent in the presence of comorbid N-ERD than without [36]. Omalizumab has been shown to improve, in parallel, respiratory parameters, sinonasal clinical outcomes, and sinus computed tomography images [37], and has significantly improved the UPSIT score and mean daily sense of smell [38]. In 2021, Han et al [39] published phase 3 results for mepolizumab in patients with CRSwNP and at least 1 previous nasosinusal surgery, demonstrating an improvement in polyp size, nasal symptoms (nasal obstruction, loss of smell), severity of disease by VAS, quality of life (SNOT-22), and a reduction in the use of SCS and the need for further surgery. However, the UPSIT score did not improve with this agent [39]. Benralizumab was recently compared with placebo in 207 patients. The authors reported a significant improvement in SNOT-22 score, polyp size, and nasal congestion, as well as a reduction in the need for surgery, although the UPSIT score did not decrease [40]. Recently, an indirect comparison between biologic treatments in CRSwNP showed dupilumab to be consistently associated with improvement in key CRSwNP outcomes with respect to omalizumab at week 24 [19,41].

A network meta-analysis comparing the efficacy and safety of monoclonal antibodies for CRSwNP reported evidence of moderate-to-high certainty that dupilumab, omalizumab, and benralizumab improved olfaction (as measured using the UPSIT) compared with placebo [42]. Among monoclonal antibodies, dupilumab seems to improve olfaction compared with omalizumab, mepolizumab, and benralizumab [42].

A review of the literature found no studies on the effects of reslizumab on olfaction. No studies differentiate between partial and total improvement, and none provide data on how many patients achieved normosmia. No previous head-to-head, real-life studies have published results on olfaction.

Based on our data, atopy and severe CRSwNP (SCS and higher polyp grade) are the factors that identify patients whose olfaction could improve with an anti-IgE or anti–IL-5 biologic, as a similar improvement in olfaction was present with all the biologics studied. In our study, the BEC did not seem to determine which patients experienced an improvement in olfaction, because although the mean BEC of the total improvement group was significantly higher than that of patients with partial improvement, it is similar to the mean BEC from the no improvement group. The relevance of these results should be explored in future studies with larger samples.

Our data show improved control of CRSwNP and asthma, as patients who experienced a total improvement in olfaction experienced a significant decrease in yearly asthma exacerbations during biologic treatment; this contrasts with the findings on disease control in the partial improvement and no improvement groups. A significant amount of available clinical evidence indicates that an improvement in CRSwNP translates into improvement in asthma control.

In summary, this is the first study to directly compare real-life improvement in sense of smell among patients undergoing long-term treatment with omalizumab, mepolizumab, reslizumab, or benralizumab for severe asthma and associated CRSwNP based on the concept of united airway diseases. Approximately 4 out of 10 patients with severe asthma reported an improvement in their subjective sense of smell (with nonsignificant differences between biologic drugs), and 18% achieved normosmia.

The limitations and strengths of the study are described in the supplementary material.

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Conflicts of Interest

Dr Alobid reports personal fees from Novartis, personal fees from Sanofi, personal fees from Menarini, personal fees from Roche, personal fees from GSK, and personal fees from MSD outside the submitted work.

Dr Olaguibel reports grants from Sanofi, personal fees from Mundipharma, personal fees from AstraZeneca, personal fees from ALK, and personal fees from GSK outside the submitted work.

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Dr Sastre reports grants and personal fees from Sanofi, personal fees from GSK, personal fees from Novartis, personal fees from AstraZeneca, personal fees from Mundipharma, and personal fees from FAES Farma outside the submitted work.

Dr Valverde-Monge reports personal fees for lectures from GSK outside the submitted work.

Dr Mullol reports personal fees and other payments from Sanofi-Genzyme and Regeneron, personal fees and other payments from Novartis, personal fees and other payments from Allakos, grants and personal fees from Mylan Pharma, grants and personal fees from Uriach Group, personal fees from Mitsubishi-Tanabe, personal fees from Menarini, personal fees from UCB, personal fees from AstraZeneca, personal fees from GSK, and personal fees from MSD outside the submitted work.

Dr Quirce reports personal fees from AstraZeneca, personal fees from Novartis, personal fees from Sanofi, personal fees from Boehringer Ingelheim, personal fees from Teva, personal fees from ALK, personal fees from Mundipharma, personal fees from GSK, personal fees from Chiesi, and personal fees from Leti outside the submitted work.

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The remaining authors declare that they have no conflicts of interest.

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