

Smell improvement by anti-IgE and anti-IL 5 biologics in patients with CRSwNP and severe asthma. A real life study

Brief running title: Smell improvement in CRSwNP induced by biologics

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Abstract

Background. Chronic rhinosinusitis with nasal polyps (CRSwNP), characterized by partial (hyposmia) or total (anosmia) loss of smell, is commonly associated with asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD), worsens disease severity and quality of life.

Objectives. The objective of this study was to determine whether, in real-life conditions, biological treatments prescribed for severe asthma can improve olfaction in patients with CRSwNP. A further objective was to compare smell improvement in N-ERD and non-N-ERD subgroups.

Methods. A multicenter, non-interventional, retrospective, observational study was performed, including 206 patients with severe asthma undergoing biological treatment (omalizumab, mepolizumab, benralizumab, or reslizumab) with CRSwNP.

Results. Improved olfaction was found after treatment with all monoclonal antibodies: omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between groups. Patients with atopy, greater use of short course systemic corticosteroids, and larger polyp size were more likely to experience improvement in smell. The proportion of patients experiencing smell improvement was similar between the N-ERD (37%) and non-N-ERD (35.7%) groups.

Conclusions. This is the first study to 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. Approximately 4 out of 10 patients reported a subjective improvement in sense of smell (with non-significant differences between biologic drugs). No differences were found in smell improvement between the N-ERD and non-N-ERD group.

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 o reslizumab).

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 nasals. Olfato. Omalizumab. Reslizumab. Olor.

INTRODUCTION

Chronic rhinosinusitis (CRS) can be divided into two main phenotypes: with (CRSwNP) and without (CRSSNP) nasal polyps. CRSwNP is commonly associated with asthma and/or nonsteroidal anti-inflammatory drug-exacerbated respiratory disease (N-ERD) [1,2]. This multimorbidity worsens CRSwNP severity 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 (hyposmia) or total (anosmia) loss of smell, which have a negative impact on patient quality of life [5].

Approximately 80% of cases are driven by type 2 inflammation, 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, which is strongly associated with asthma and loss of smell [7], contrasts with non-eosinophilic inflammatory endotype.

The sense of smell is a constant source of valuable information for humans, enabling them to detect harmful odors as well as enjoy pleasurable experiences. Loss of smell is a quantitative dysfunction of olfaction as measured by hyposmia (diminished capacity of smell) and anosmia (complete absence of smell); alone, presence of this symptom has demonstrated potency as a positive predictive symptom for CRS [8,9] and it 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 severity of disease [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 of most cases of CRSwNP, specific biologic therapies targeting type 2 inflammation have been developed, including anti-IgE (omalizumab), anti-IL-5 (mepolizumab, reslizumab, benralizumab), and anti-IL-4/IL-13 (dupilumab) monoclonal antibodies [3-4]. Although some indirect comparative studies have been published [18–20], no head-to-head comparisons between biologicals have been carried out in CRSwNP.

The main purpose of this study was to determine whether, in real-life conditions, 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 (anti-IgE, anti-IL-5, and anti-IL-4/IL-13). A further objective was to analyze the N-ERD subgroup, usually the most severe pheno-endotype of CRSwNP, against non-N-ERD subjects and by arbitrarily comparing patients with different BEC levels.

1. METHODS

1.1 Study population

A multicenter, non-interventional, retrospective, observational, real-life study was performed in the allergology and pulmonology departments of 9 hospitals belonging to the Spanish Network of Asthma [21,22]. The study included 545 patients ≥ 18 years of age diagnosed with severe asthma and who were undergoing biological treatment (omalizumab, mepolizumab, benralizumab, reslizumab, dupilumab) [23] in accordance with the criteria appearing in the GINA guidelines [24], for a minimum time of 1 year. For this study, only patients with CRSwNP (diagnosed as the presence of sinonasal symptoms, nasal endoscopy and/or CT scan) [3] were selected. The dupilumab subgroup was excluded from analysis due to its small size (n=4).

2.2 Study design and ethical aspects

A retrospective review of electronic medical records was performed to collect patient data such as demographic characteristics, atopy (defined as a positive specific IgE in serum or at least one positive skin prick test 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) questionnaire, forced expiratory volume in 1 second (FEV₁), fractional exhaled nitric oxide (FeNO)], and blood eosinophil count (BEC). CRSwNP onset, use of nasal and systemic corticosteroids (SCS), 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 participating hospitals.

Olfaction was evaluated subjectively at least in two different time points – before biologic treatment and during biologic treatment- and included a binary yes/no question on the degree of smell loss: normal smell (normosmia) and partial (hyposmia) or total (anosmia) loss of smell. As data on olfaction during biological treatment were registered during the pandemic by SARS-CoV-2, which can cause hyposmia/anosmia, data on olfaction from before infection were used to avoid possible bias; on the other hand, presence of CRSwNP/eosinophilic CRS could act as a protective factor for the loss of smell induced by COVID-19 due to the downregulation of ACE2 and TMPRSS2 in the olfactory neuroepithelium of CRSwNP patients [25].

Using nasal endoscopy, polyp size was scored on a scale of 0-4 per side according to the criteria of Meltzer [26] performed by an ENT and/or allergist; the median number with its interquartile range (25%-75%) was obtained from the left and right nostril on each patient.

2.3 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” (subjects with no improvement or who experienced a deterioration in their olfaction); additionally, we analyzed these data to determine whether there was any difference between these three categories depending on the biologic treatment used. After that, we performed a sub-analysis to search for possible differences in smell improvement between the N-ERD and non-N-ERD subgroups by arbitrarily comparing patients with different BEC levels, i.e., <500 vs. \geq 500 eosinophils/ μ l and <300 vs. \geq 300 eosinophils/ μ l (cut-off point of previous studies with CRSwNP and biologics).

2.4 Statistical analysis

Categorical variables were described by absolute and relative frequencies. Quantitative variables were described by mean and standard deviation (SD) or by median and interquartile range (IQR). Categorical variables were compared using the chi-square or Fisher's exact test. Quantitative variables were compared using the Mann-Whitney U test or t-test in comparisons between 2 groups, and Kruskal-Wallis test or ANOVA when comparing 3 or more groups,

according to the normality result determined by Kolmogorov-Smirnov. Comparisons of paired samples (before biologic treatment and during biologic treatment) were performed using McNemar test for categorical variables, and paired samples Student's t test or Wilcoxon signed-rank test for quantitative variables. The effectiveness of biologics was compared, adjusting for duration of biologic and frequency of anosmia before biologic, using logistic regression models. Statistical analyses were conducted using GraphPad Prism 8 (GraphPad Software Inc, San Diego, CA, USA) and R 4.0.2 (R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria). A p-value <0.05 was considered statistically significant.

2. RESULTS

2.1 Demographic characteristics

From the initial cohort of 545 patients with severe asthma treated with a monoclonal antibody, 225 (41.3%) had CRSwNP. Fifteen subjects were excluded due to a lack of information on olfaction. The dupilumab subgroup (n=4) was also excluded from analysis due to its small sample size (Figure 1). As a result, the total sample included 206 patients (age range 56 ± 13 years, 56.8% female) (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 (Table 1). All groups were homogeneous in terms of the variables studied, except for presence of atopy, as the mepolizumab group contained significantly fewer subjects with atopy as compared to the omalizumab and reslizumab groups

($p=0.02$). Another difference concerned the time of treatment ($p=0.0001$) between almost all biologic groups except for those treated with mepolizumab and reslizumab. Ninety-two patients (44.7%) presented association with N-ERD, most of whom were treated with omalizumab (41/92).

The mean time since onset of asthma was 21 ± 13 years. In all groups, lung function as measured by FEV₁ improved after biologic treatment. The number of asthma exacerbations per year improved after all monoclonal antibody treatments. Asthma improvement was also evidenced by an increase in ACT score in all groups, including the reslizumab group, which had significantly lower ACT scores before the therapy initiation than the other groups ($p=0.001$ vs. omalizumab and mepolizumab, $p=0.03$ vs. benralizumab).

At baseline, the mean BEC of asthmatics with CRSwNP was 541 ± 369 cel/ μ L. Patients with mepolizumab had higher counts than those undergoing omalizumab ($p=0.005$) and benralizumab ($p=0.04$). After biological treatment, there was a significant decrease in BEC ($p<0.0001$) and a marked decrease in BEC can be observed in anti-IL-5 biologics compared with omalizumab ($p<0.0001$). Among anti-IL-5 biologics, eosinopenia was significantly more prevalent ($p<0.0001$) in those treated with benralizumab than those receiving mepolizumab and reslizumab.

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 and had a median score of 2 out of 4 according to Meltzer et al. [26]; other common features were use of short courses of SCS (1.7 ± 2 cycles per year) and median number of 1 EES (0-2). During monoclonal treatment, there was a

significant reduction in polyp size (overall, $p < 0.0001$), use of SCS (overall, $p < 0.0001$), and need for EES (overall, $p < 0.0001$) in the groups receiving omalizumab, mepolizumab, and benralizumab. Reslizumab subjects showed a statistically significant decrease in the number of EES ($p = 0.0039$); although a reduction was observed in polyp size ($p = 0.9041$) and SCS use ($p = 0.0625$) from baseline to the time after administration of reslizumab, these changes did not reach statistical significance (Table 2).

Regarding olfaction, pre-treatment presence of hyposmia and normosmia was homogenous between groups of biologics, but significant differences were observed in terms of anosmia. The omalizumab and mepolizumab groups had significantly more subjects with anosmia in comparison to the group treated with benralizumab ($p = 0.03$ and $p = 0.04$, respectively), both before and after biologic treatment. A comparison of olfaction from baseline to after biologic use showed an increase in subjects with normosmia that reaches statistical significance when the entire sample is analyzed ($p = 0.0004$); however, when biologic groups were compared, only the increase of normosmia in the omalizumab group reached statistical significance ($p = 0.041$). The significant drop in subjects with anosmia from baseline to after biologic treatment was noteworthy ($p < 0.0001$) throughout the sample. This decrease was also statistically significant in all groups except the reslizumab group (Figure 2).

3.2. Improvement in olfaction

A total or partial improvement in loss of smell was found after treatment with all monoclonal antibodies: omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between groups (Figure 3). Approximately 61% to 64% of patients

experienced no improvement, and no statistical differences were found between biologic treatments.

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

An analysis of subjects with and without smell improvement after therapy revealed certain pre-treatment differences in sociodemographic and clinical variables (Table 3). Patients with atopy, increased use of SCS short cycles, and greater nasal polyp size were more prone to experience improvement in smell. There were no differences between the drugs in terms of their efficacy (improvement vs no improvement) adjusting for duration of biologic and frequency of anosmia before biologic.

Between groups experiencing total or partial improvement, a striking difference in mean BEC before treatment was observed, as those patients who experienced total improvement had significantly a higher BEC ($p=0.05$) but similar to the BEC of the no improvement group ($p=0.52$). Also, the partial improvement group needed more EES ($p=0.01$) than the total improvement group, though this level was similar that of the no improvement group ($p=0.13$) (Table 3).

After biologic treatment, asthma exacerbations were less frequent in the total improvement vs the no improvement group ($p=0.008$), while INCS (intranasal corticosteroids) were more commonly prescribed in the partial improvement group than the total improvement ($p=0.02$) and the no improvement ($p=0.008$) groups (Table 3).

3.3 N-ERD analysis

It is worth noting that of the total subjects with anosmia before biologic treatment with omalizumab or mepolizumab, N-ERD explains 66% and 52% of anosmia; in contrast with 35% N-ERD subjects with anosmia in the benralizumab group; this could explain the difference among them.

The N-ERD and non-N-ERD groups were comparable in terms of demographics, onset of asthma, duration of biologic treatment, lung function and FeNO, control of asthma, and asthma exacerbations. The mean BEC between both groups was also similar before and after biologic therapy (Table 4).

Concerning the baseline characteristics (before biologics) of CRSwNP disease, N-ERD patients were more likely to develop CRSwNP than non-N-ERD, had greater smell impairment (fewer subjects with normosmia) than non-N-ERD, and a showed higher number of EES than non-N-ERD. No differences were found in nasal polyposis size, use of SCS, or INCS.

After biologic treatment, the proportion of subjects with normosmia was higher in the non-N-ERD as compared to the N-ERD group. The proportion of patients experiencing smell improvement was similar in N-ERD (37.0%) and non-N-ERD (35.7%). Total (17.4% with N-ERD vs 18.3% with non-N-ERD) and partial (19.6% with N-ERD vs 17.4% with non-N-ERD) smell improvement was also similar between groups.

3.4 Blood eosinophil count (BEC) analysis

On smell analysis, the comparison of total improvement, partial improvement and no improvement between subjects with high vs low BEC (<500 vs \geq 500 cell/ μ l) was not statistically different. No statistical differences were found among the different biologic groups. Using the BEC cut-off (< 300 vs \geq 300 cell/ μ l) no differences were found in total, partial, or no smell improvement between BEC groups.

4. DISCUSSION

The demographic characteristics of this asthma severe cohort (age 56 ± 13 years, 56.8% female, 41.3% with CRSwNP and 44.7% with N-ERD) resemble those from previous reports [27,28]. The differences found in mean time of treatment with biologics between almost all biological 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 of the improvement in smell, this fact does not seem to be relevant.

In our sample with 51.9% of patients with anosmia and 33.3% of hyposmia, smell improvement was found in 35% to 39% of patients: omalizumab (35.8%), mepolizumab (35.4%), reslizumab (35.7%), and benralizumab (39.1%), with no differences between the monoclonal antibodies in total or partial improvement, so regardless of the duration of treatment, or the percentage of patients with initial anosmia. Smell improvement was more common in patients with atopy, higher use of SCS short cycles, and 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.

After biological treatment, BEC was reduced in all cases, more strongly with mepolizumab, benralizumab, and reslizumab; this was expected due to their different mechanisms of action. As omalizumab does not target eosinophil function nor programmed apoptosis in eosinophils, BEC does not develop as intensely as with anti-IL-5 treatments [29–31].

As we can observe, our sample meets the clinical characteristics of the T2 endotype as described by Stevens et al [7].

N-ERD and non-N-ERD were comparable groups in terms of demographic characteristics, asthma profile, and mean BEC. N-ERD had a negative impact on smell (fewer subjects with normosmia) and a higher need for EES, which is consistent with the poor response to INCS and SCS described in literature [2–4]. Smell improvement was similar in N-ERD (37.0%) and non-N-ERD patients

(35.7%), with no differences was associated with partial or total improvement which contrasts 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], and therefore blood eosinophilia has been correlated with eosinophilic inflammation endotype [33] and is used to diagnose eosinophilic CRS. The Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis evaluated BEC and eosinophils in tissue of 1716 EES patients and concluded that BEC was associated with recurrence of disease and need for further surgical intervention but not with improvement in smell [34]. In our study, no differences related to improvement of smell were found depending on blood eosinophilia, both when cutoff points of 300 and 500 cell/ μ L were applied.

This long-term (mean 3.7 ± 2.6 years), head-to-head, real-life study shows that 36.1% of patients with severe asthma and associated CRSwNP experienced an improvement in olfaction. N-ERD subjects showed a similar improvement in smell (35.7%) to those without N-ERD (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 been shown to improve smell with high effectiveness as evaluated by means of the University of Pennsylvania Smell Identification Test (UPSIT) score, and quality of life evaluated using the Sino-Nasal Outcome Test (SNOT-22), with a mean difference of -19.14 [95% CI $(-22.80$ to $-15.47)$][35]. In two randomized placebo-

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controlled phase 3 trials with patients with uncontrolled severe CRSwNP, dupilumab significantly improved objective measures (nasal polyp score, total symptom score, and rhinosinusitis severity visual analog scale -VAS-) and patient-reported symptoms to a greater extent in the presence of comorbid NSAID-ERD than without [36]. Omalizumab has demonstrated to improve, in parallel, respiratory parameters, sinonasal clinical outcomes and sinus computed tomography images [37] and also a significant amelioration in UPSIT score and mean daily sense of smell (mean difference: +3.84; 95% CI +3.64 to +4.04) [38]. In 2021, Han et al. published the phase 3 of mepolizumab (100 mg, subcutaneously, every 4 weeks) for 52 weeks, in patients with CRSwNP with at least one previous nasosinus surgery demonstrating an improvement in the size of the polyps, 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, but did not improve UPSIT score [39]. Benralizumab has been recently evaluated in 207 patients vs placebo which revealed a significant improvement in SNOT-22 score, polyp size, nasal congestion and reduction in need of surgery, but not in UPSIT reduction [40]. Recently, an indirect treatment comparison between biologic treatments in CRSwNP has demonstrated that dupilumab is consistently associated with greater improvement in key CRSwNP outcomes versus omalizumab at week 24 [19,41].

A network meta-analysis comparing efficacy and safety of monoclonal antibodies for CRSwNP has concluded that there was moderate to high certainty evidence that dupilumab, omalizumab, and benralizumab improve smell measured by UPSIT compared to placebo [42]. Among monoclonal antibodies, dupilumab likely improves smell as compared with omalizumab, mepolizumab, and benralizumab [42].

A review of the literature found no studies on the effects of reslizumab on sense of smell. No

studies differentiate between partial and total improvement, and none provide data on how many patients reached normosmia. No previous head-to-head, real-life studies have published results on sense of smell.

Based on our data, subjects with atopy and severe CRSwNP disease (SCS and higher polyp grade) are the factors that identify subjects who could experience an improvement in smell when treated with an anti-IgE or anti-IL-5 biologic, as similar olfaction improvement was present with all biologics studied. In our study, BEC did not seem to determine which subjects improve their smell, 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 sample sizes.

In our data there is an improve in control of CRSwNP and also in asthma control, as subjects with total improvement in smell experienced a significant decrease in yearly asthma exacerbations during biologic treatment; this contrasts with the findings on disease control in the partial improvement or no improvement groups. A significant amount of clinical evidence already available supports that an improvement in CRSwNP disease translates to 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, under the United Airway Disease concept. Approximately 4 out of 10 included patients with severe asthma reported an

improvement in subjective sense of smell (with non-significant differences between biologic drugs), 18% of them reaching normosmia.

LIMITATIONS/STRENGTHS

The main bias of the study is that smell was not evaluated objectively (i.e., olfactometry) because its retrospective nature. As it is a real-life study, the data between biologicals are not compared in a single treatment time horizon, but the last olfaction data is collected. Data on diagnosis of N-ERD were also gathered from the clinical history (past history of reactions to NSAIDs) rather than acetylsalicylic acid challenge.

The strengths of this study include its multicenter design with a large sample of patients receiving biological treatment. Additionally, this is the first study in a single airway (smell in asthma, CRSwNP with/without ERD).

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Conflict of interest statement

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Dr. Mullol reports personal fees and other from Sanofi- Genzyme & Regeneron, personal fees and other from Novarits, personal fees and other 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, personal fees from MSD, outside the submitted work.

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Accepted Article

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Figure 1. Changes in olfaction: no improvement, partial (change from anosmia to hyposmia) and total (from anosmia or hyposmia to normosmia) smell improvement.

No statistically significant difference was found between normosmia, hyposmia, and anosmia groups when treated with each biologic.

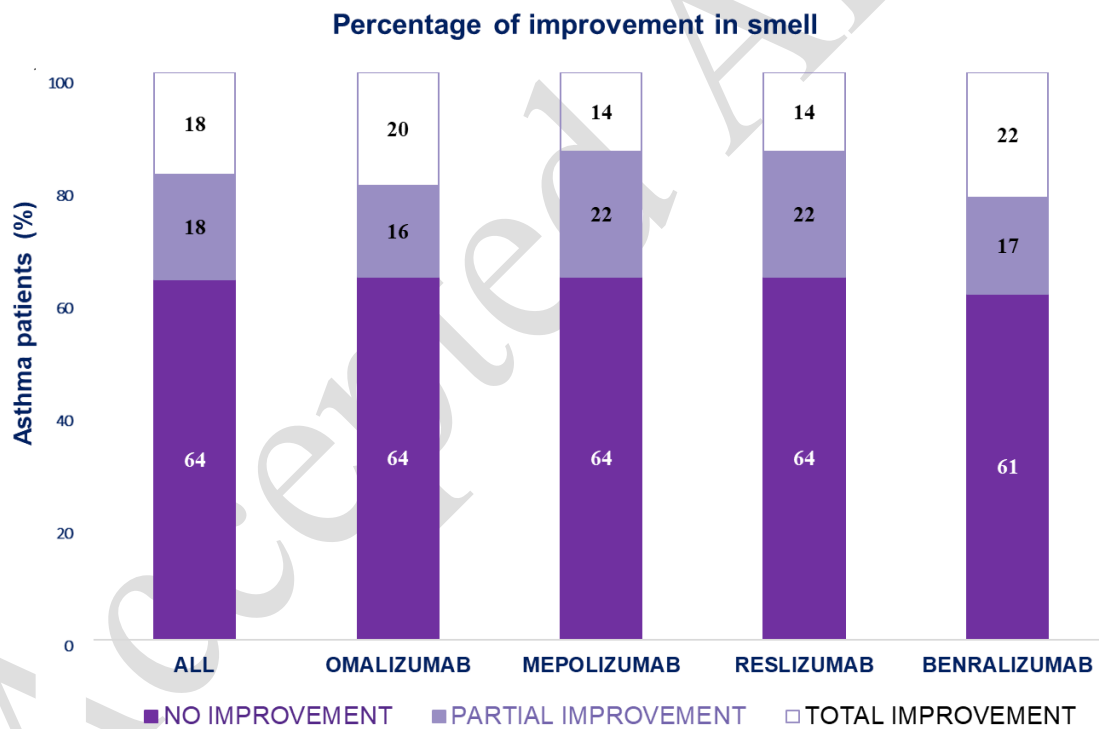


Table 1. Data about asthma, blood eosinophils count, CRSwNP and smell, before and during biologic treatment.

	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
FEV ₁ (%), (mean±SD)	71.2 ± 24.6	74.8 ± 30.5	<0.0001	74.0 ± 21.4	86.6 ± 21.1	<0.0001	63.0 ± 22.8	78.3 ± 19.5	0.0003	58.6 ± 31.2	80.2 ± 20.2	0.0140	73.0 ± 18.2	79.8 ± 19.4	<0.0001
FeNO ppb, (mean±SD)	65.0 ± 53.1	49.2 ± 45.7	0.0008	58.2 ± 38.6	40.4 ± 38.8	<0.0001	72.3 ± 65.7	47.8 ± 37.3	0.0212	59.5 ± 38.8	75.4 ± 52.6	0.3105	63.3 ± 53.7	58.5 ± 61.8	0.6444
ACT questionnaire, (mean±SD)	16.1 ± 5.8	22.3 ± 5.4	<0.0001	17.2 ± 15	21.7 ± 3.3	<0.0001	16.1 ± 4.5	22.2 ± 2.8	<0.0001	12.4 ± 4.7	24.2 ± 1.4	0.0002	16.4 ± 6.6	22.2 ± 4.3	<0.0001
Asthma exacerbations per year	3.1 ± 2.4	0.5 ± 1	0.0007	3.3 ± 2.7	0.5 ± 0.7	<0.0001	4.2 ± 2.1	0.7 ± 0.9	<0.0001	3.71 ± 1.8	0.1 ± 0.4	<0.0001	3.1 ± 2.1	0.5 ± 1.4	<0.0001
BEC, cel/μL (mean±SD)	541± 369	186 ± 239	<0.0001	477 ± 315	368 ± 274	0.0045	652 ± 410	92 ± 84	<0.0001	529 ± 355	63 ± 42	0.0015	509 ± 379	6 ± 20	<0.0001
Normosmia, N (%)	29 (14.1)	62 (30.1)	0.0004	7 (8.6)	22 (27.2)	0.0041	11 (16.9)	19 (29.2)	0.1642	2 (14.0)	4 (28.57)	0.6451	9 (19.6)	17 (37)	0.1695
Hyposmia, N (%)	70 (33.3)	88 (42.7)	0.0678	26 (32.1)	29 (35.8)	0.7400	17 (26.3)	27 (41.5)	0.0953	5 (35.7)	8 (57.14)	0.4485	22 (47.8)	24 (52.2)	0.6766
Anosmia, N (%)	107 (51.9)	56 (25.7)	<0.0001	48 (59.2)	30 (37.1)	0.0075	37 (56.9)	19 (29.2)	0.0026	7 (50.2)	2 (14.3)	0.1055	15 (32.6)	5 (11.6)	0.0229
Grade of polyposis (0-4), median	2 (0-4)	1 (0-4)	<0.0001	2 (0-4)	1 (0-3)	<0.0001	2 (0-4)	1 (0-4)	0.0013	2 (0-4)	2 (0-3)	0.9041	2 (0-4)	1 (0-4)	<0.0001
Use of intranasal corticosteroids,	198 (91.9)	198 (96.1)	0.0126	80 (98.8)	74 (91.4)	0.0698	59 (90.8)	54 (83)	0.2981	12 (85.7)	12 (85.7)	0.5892	43 (93.5)	38 (82.6)	0.7813
Systemic corticosteroids, short	1.7 ± 2	0.4 ± 0.8	<0.0001	2 ± 2.5	0.4 ± 0.8	<0.0001	2 ± 2.2	0.5 ± 0.8	<0.0001	1.4 ± 2.2	0.1 ± 0.3	0.0625	1 ± 1	0.3 ± 0.8	<0.0001
EES per year, median (IQR)	1 (0-2)	0 (0-2)	<0.0001	1 (0-2)	0 (0-2)	<0.0001	1 (0-2)	0 (0-1)	<0.0001	1 (0-2)	0	0.0039	1 (0-2)	0 (0-1)	<0.0001

Pre (before biologic treatment); Post (during biologic treatment); FEV₁ (forced expiratory volume in 1 second); SD (standard deviation); FeNO (fractional exhaled nitric oxide); ACT (asthma control test questionnaire); BEC (blood eosinophil count); IQR (interquartile range); EES (endoscopic endonasal *surgery*).