

Effects of Omalizumab Treatment in Patients With Recalcitrant Nasal Polyposis and Mild Asthma: A Multicenter Retrospective Study

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Abstract

Background: Chronic rhinosinusitis with nasal polyps (CRSwNP) is a clinical entity with specific features that impacts significantly on patient quality of life (QoL). CRSwNP is often associated with asthma and is difficult to control and manage despite pharmacological and/or surgical treatment. Omalizumab, a monoclonal anti-IgE antibody, has emerged as a putative therapeutic option.

Objective: To evaluate the effects of omalizumab on nasal polyp (NP) size and QoL assessed by Sino-Nasal Outcome Test-22 (SNOT-22) in patients with recalcitrant CRSwNP and mild asthma.

Methods: A multicenter retrospective analysis of patient data from the Community of Valencia (Spain) was performed. Adult patients with recalcitrant CRSwNP and comorbid mild asthma receiving compassionate use of omalizumab were included. NP size measured by total nasal endoscopic polyp score (TPS) and QoL evaluated through the SNOT-22 questionnaire were assessed at baseline and monthly over 12 months. An ordinal regression model was built to analyze the results.

Results: A total of 23 CRSwNP patients with a mean age ($\pm$ SD) of 54.78 ± 9.46 years were included. Nineteen suffered from aspirin-exacerbated respiratory disease (AERD). In all patients, a significant and sustained reduction in TPS was observed over time, accompanied by improvements in QoL reflected in lower SNOT-22 scores. In the ordinal regression model, time but not total IgE, age or tissue eosinophilia impacted on NP size and SNOT-22 outcomes. Additionally, improvements in QoL were not explained by reductions in the size of polyps.

Conclusion: Omalizumab was effective for the treatment of patients with recalcitrant CRSwNP and mild asthma, even when AERD was present, by reducing NP size and improving QoL; treatment time was a key factor. SNOT-22 improvements were not explained by decreases in TPS, indicating that omalizumab may be effective in all patients, regardless of polyp size.

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chronic rhinosinusitis with nasal polyps, nasal polyps, mild asthma, omalizumab, aspirin-exacerbated respiratory disease, total nasal endoscopic polyp score, SNOT-22, quality of life, IgE, tissue eosinophilia

Introduction

Chronic rhinosinusitis (CRS) with nasal polyps (CRSwNP) is a subtype of CRS with specific features that must be diagnosed and treated as an independent clinical entity.¹ It is a chronic inflammatory condition of the mucosa covering the sinonasal cavities accompanied by benign lesions of uncertain etiology typically arising from the ethmoid sinus.² Clinically, nasal obstruction/congestion is the most frequent symptom, which may be accompanied by smell disturbance.³

The global prevalence of nasal polyposis is estimated to be as high as 1% to 4%.^{4,5} Because of chronicity, risk of exacerbations, and frequent recurrence despite pharmacological or surgical treatment, they have a considerable impact on patient quality of life (QoL) and are a major economic burden on society.⁶

The association of NP with other pathologies such as asthma and aspirin sensitivity is well documented. In fact, in asthma patients, the prevalence of CRSwNP is higher than in the overall population (7% vs. 4%), while the presence of asthma in patients with CRSwNP is above 45%.⁷ Aspirin-exacerbated respiratory disease (AERD) is present in 10% of asthma patients with CRSwNP, and is the most severe presentation of this disease.⁸ In 85% of CRSwNP patients an activation of the Th2 lymphocyte-mediated inflammatory cascade is evident, characterized by an eosinophilic profile accompanied by high levels of IgE and IL-5.⁹ In these patients, the grade of tissue inflammation and the amount of local IgE are independent of the presence of allergy. However, the presence of asthma is associated with increased local IgE levels,¹⁰ apparently induced by *Staphylococcus aureus* enterotoxins and combined with severe eosinophilic inflammation.¹¹ In fact, enterotoxins are frequently found in asthma patients with NP.¹² Given the difficulty in managing and controlling patients with CRSwNP and asthma with conventional treatments and/or surgery, new therapeutic options are needed. Biologics have emerged as a promising alternative for these patients, among which omalizumab, a monoclonal anti-IgE antibody has already demonstrated potential benefits in patients with CRSwNP and moderate/severe asthma.^{13–16} However, the efficacy in cases of mild asthma, in which omalizumab would only be indicated for NP, has not yet been assessed. Currently, omalizumab is indicated for the treatment of IgE-mediated

severe asthma and chronic urticaria. It inhibits the binding of IgE to its receptor (FcεRI) present in mast cells and basophils, inhibits the activation of IgE already bound to mast cells and prevents their degranulation, and downregulates FcεRI expression.^{17,18} In recalcitrant CRSwNP with mild asthma, omalizumab in combination with conventional treatment with corticosteroids might significantly ameliorate disease by reducing NP size, symptom severity, and improve QoL.

The aim of this study was to evaluate the effects of omalizumab treatment on NP size and QoL assessed by Sino-Nasal Outcome Test-22 (SNOT-22) in patients with recalcitrant CRSwNP and mild asthma. Secondary objectives include the analysis of their possible association with other variables such as total serum IgE levels and tissue eosinophilia.

Methods

Study Design

A multicenter retrospective analysis from six hospitals from the community of Valencia (Spain) (University and Polytechnic La Fe Hospital, University General Hospital of Valencia, Arnau de Vilanova Hospital, Valencia Manises Hospital, Clinic University Hospital of Valencia and Sagunto Hospital) was performed between January 2016 and September 2019. The study was approved by the University and Polytechnic La Fe Hospital's Clinical Research and Ethics Committee. All patients provided written informed consent before participation.

Patients

Patients with recalcitrant CRSwNP and comorbid mild asthma receiving compassionate use of omalizumab were included. Inclusion criteria were nasal polyposis not controlled with standard maximum therapy, age between 18 and 75 years, diagnosis of mild bronchial asthma according to GEMA criteria,¹⁹ presence of AERD (both AERD and non AERD patients were allowed to participate), two or more prior endonasal surgeries, total serum IgE levels before omalizumab treatment >30 kU/L, nasal endoscopic score ≥1 in each nasal cavity as shown by Gevaert et al.,¹³ three or

more cycles of systemic corticosteroid per year. Patients not meeting these criteria were excluded from the study.

Interventions and Outcomes

The period between the last surgery and the start of omalizumab treatment ranged between 11 and 47 months, with an average of 23 months. The dose (in milligrams) of omalizumab (Xolair®; Novartis, Basel, Switzerland) administered monthly was based on total serum IgE levels (in international units per milliliter) and body weight (in kilograms). Prior to drug administration, total serum IgE levels, NP size measured by the total nasal endoscopic polyp score (TPS) as well as a NP biopsy after at least two weeks with no topic or systemic corticosteroid treatment to determine tissue eosinophilia (defined as % of eosinophils/total number of inflammatory cells²⁰) were performed. To assess health status and health-related QoL, patients were also asked to complete the SNOT-22 questionnaire on their first visit.²¹ Possible SNOT-22 total scores range from 0 to 110, with higher total scores indicating worse symptoms. Monthly visits were scheduled over 12 months, in which endoscopic scores and SNOT-22 values were registered.

All patients also received treatment with mometasone furoate nasal spray 100 micrograms in each nostril every 12 hours throughout the study. No other additional treatments were prescribed.

Statistics

Continuous variables were expressed as mean and standard deviation (SD) and categorical variables as absolute and relative frequencies. A Bayesian ordinal regression model was used to evaluate the effect of omalizumab on NP size and SNOT-22 score over time.²² This model also considered other variables of interest such as age, IgE total and eosinophilia. Given the longitudinal nature of the study and the non-independence of the observations, a slope for time and an independent term for each patient was included.²³ Furthermore, as the effect of omalizumab over time was not expected to be linear, time was included in the model as a monotonic effect.²⁴

All statistical analysis were conducted using R software version 3.6.1, brms package version 2.10.0 and clickR package version 0.4.39. The interpretation of the effects was made based on Bayesian credibility interval estimations to 95% for each of the parameters.

Results

A total of 23 CRSwNP patients with a mean age (SD) of 54.78 (9.46) years were included. Patient baseline characteristics are summarized in Table 1.

Table 1. Patient Baseline Characteristics.

Variables	N = 23
Sex; n (%)	
Male	12 (52.17)
Female	11 (47.83)
Age, years Mean (SD)	54.78 (9.46)
Median (IQR)	55 (48.5–63)
SNOT-22 total score Mean (SD)	58.96 (25.36)
Median (IQR)	55 (44.5–73.5)
Total serum IgE (IU/mL) Mean (SD)	246.04 (248.96)
Median (IQR)	145 (97–307.5)
Eosinophilia % eosinophils/ total n° inflammatory cells	
Mean (SD)	53.57 (29.8)
Median (IQR)	50 (30–70)
AERD	
No	4 (17.39%)
Yes	19 (82.61%)
NP staging (RNC)*; n (%)	
P1	1 (4.35)
P2	9 (39.13)
P3	11 (47.83)
P4	2 (8.7)
NP staging (LNC)*; n (%)	
P1	1 (4.35)
P2	9 (39.13)
P3	10 (43.48)
P4	3 (13.04)

AERD, aspirin-exacerbated respiratory disease; **IQR**, interquartile range; **LNC**, left nasal cavity; **NP**, nasal polyps; **RNC**, right nasal cavity; **SD**, standard deviation; **SNOT-22**, sino-nasal outcome test-22.

*According to Gevaert et al. criteria.¹³

Nasal Polyp Size

NP size was evaluated over 12 months of omalizumab treatment. As observed in Table 2 and Figure 1, this drug improved TPS values over the course of the study. An ordinal regression model was used to assess the actual effect of time on NP size, as well as the putative influence of other variables such as age, total IgE and eosinophilia. As expected, time was associated with NP size (OR = 0.61, [95% CI: 0.478, 0.735]). However, other analyzed factors did not show any influence on this variable (Supplementary Table S1).

QoL Measured by the SNOT-22

When QoL was evaluated using the SNOT-22 questionnaire, similar results for NP size were obtained. Thus, scores decreased over 12 months, indicating an improvement with omalizumab treatment (Table 3 and Figure 2). In the ordinal regression model, time was strongly associated with SNOT-22 values over time (OR = 0.46, [95% CI: 0.369, 0.561]), while age, total IgE and eosinophilia

Table 2. Nasal Polyp Size Evolution Over 12 Months of Omalizumab Treatment.

NP size	Baseline	M 1	M 2	M 3	M 4	M 5	M 6	M 7	M 8	M 9	M 10	M 11	M 12
RNS*, n (%)													
P0	0 (0)	0 (0)	0 (0)	2 (9.52)	3 (17.65)	1 (6.25)	3 (15.79)	1 (7.14)	0 (0)	0 (0)	1 (4.55)	0 (0)	0 (0)
P1	1 (4.35)	5 (27.78)	2 (12.5)	7 (33.33)	6 (35.29)	8 (50)	7 (36.84)	4 (28.57)	6 (40)	6 (40)	8 (36.36)	6 (37.5)	6 (35.29)
P2	9 (39.13)	9 (50)	9 (56.25)	10 (47.62)	7 (41.18)	5 (31.25)	6 (31.58)	6 (42.86)	6 (40)	7 (46.67)	6 (27.27)	8 (50)	9 (52.94)
P3	11 (47.83)	4 (22.22)	4 (25)	2 (9.52)	1 (5.88)	2 (12.5)	3 (15.79)	3 (21.43)	3 (20)	2 (13.33)	7 (31.82)	2 (12.5)	2 (11.76)
P4	2 (8.7)	0 (0%)	1 (6.25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
LNS*, n (%)													
P0	0 (0%)	0 (0)	1 (6.25)	3 (14.29)	2 (11.76)	2 (12.5)	2 (10.53)	0 (0)	0 (0)	0 (0)	2 (9.09)	0 (0)	0 (0)
P1	1 (4.35)	5 (27.78)	4 (25)	6 (28.57)	6 (35.29)	4 (25)	5 (26.32)	4 (28.57)	3 (20)	2 (13.33)	4 (18.18)	7 (43.75)	7 (41.18)
P2	9 (39.13)	8 (44.44)	5 (31.25)	8 (38.1)	5 (29.41)	5 (31.25)	9 (47.37)	6 (42.86)	8 (53.33)	10 (66.67)	11 (50)	4 (25)	10 (58.82)
P3	10 (43.48)	5 (27.78)	5 (31.25)	4 (19.05)	4 (23.53)	5 (31.25)	3 (15.79)	4 (28.57)	4 (26.67)	3 (20)	4 (18.18)	5 (31.25)	0 (0)
P4	3 (13.04)	0 (0)	1 (6.25)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (4.55)	0 (0)	0 (0)

LNC, left nasal cavity; M, month; NP, nasal polyps; RNS, right nasal cavity.

*According to Gevaert et al. criteria.¹³

showed no influence on this variable (Supplementary Table S2).

A new ordinal regression model that included NP size at every time point (monthly measurements) was used to determine whether improvements in the QoL measured by the SNOT-22 questionnaire over time could be explained by the concomitant NP size reduction observed. Results did not provide evidence to support that the improvement over time experienced in SNOT-22 results (Figure 3) was influenced by NP size (OR NP Size*Time = 1.008 [0.966, 1.08]) (Supplementary Table S3).

Discussion

The efficacy of omalizumab for the treatment of CRSwNP patients has been demonstrated in two phase III clinical trials carried out in adult patients with corticosteroid-refractory NP.²⁵

In our study, patients sharing two specific and significant clinical features not previously assessed were analyzed. On the one hand, patients suffered from mild asthma and consequently not considered eligible for omalizumab treatment were included. This is important, as most studies have been conducted in patients with CRSwNP and severe asthma.²⁶ On the other hand, patients presented recalcitrant polyposis, suffered from AERD in most of the cases, and had been previously subjected to at least two prior surgeries with poor control of their disease, stressing the severity of the polyposis. Our results indicate that omalizumab was also effective in this context, regardless of total IgE levels and tissue eosinophilia. Furthermore, our sample size was in line with similar studies^{13,15,16,27,28} and meta-analyses,²⁶ showing the importance of the conclusions obtained. The latest literature reviews on nasal polyposis treatment with biologics stress the small sample size and heterogeneity of the results obtained in the studies included.²⁹ In contrast, our study sample was homogeneous, and results were consistent and clinically relevant, with no exceptions registered for any of the participants.

The decision to perform new surgical interventions or to start treatment with biologics (omalizumab in our study) should be evaluated according to cost-efficiency. In an extensive review of the cost-effectiveness of surgery vs. medical treatment (such as steroids and antibiotics), the authors did not find any evidence supporting either treatment.³⁰ However, treatments with biologics were not included in this review, and the quality of the studies analyzed is probably insufficient for drawing solid conclusions. This highlights the need for further analyses that should specifically focus on the cost-effectiveness of biological therapies, as recently claimed by other authors.³¹ Regarding the decision to perform new surgical interventions or to start treatment with biologics,

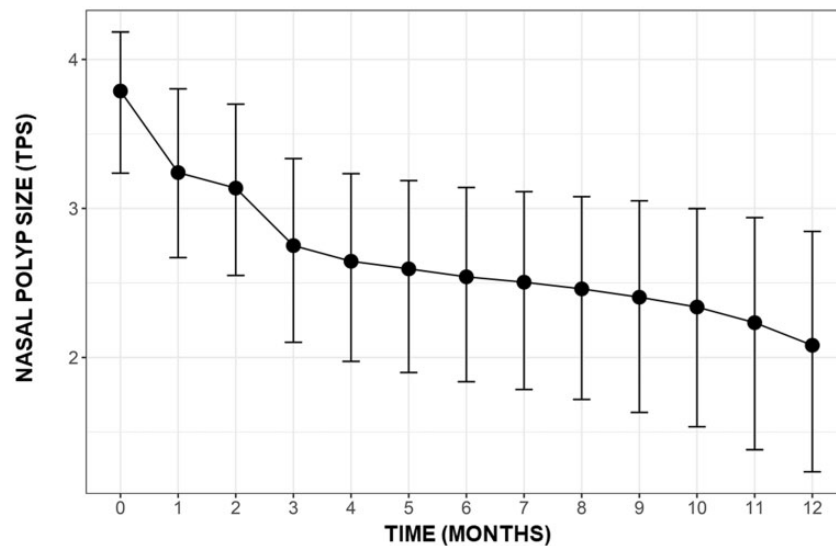


Figure 1. Nasal polyp size measured by total nasal endoscopic score (TPS) over 12 months of omalizumab treatment.

Table 3. SNOT-22 Scores Over 12 Months of Omalizumab Treatment.

Time (Months)	SNOT-22 Scores	
	Mean (SD)	Median (IQR)
Baseline	58.96 (25.36)	55 (44.5–73.5)
Month 1	39.56 (24.55)	38 (22.5–51)
Month 2	40 (22.77)	35.5 (22–54)
Month 3	36 (27.74)	29 (15–51)
Month 4	22.88 (15.59)	24 (8–30)
Month 5	24.56 (15.76)	25 (7–36.25)
Month 6	24.89 (20.09)	15 (10–37.5)
Month 7	27.14 (20.34)	24 (10–39)
Month 8	22.53 (18.93)	18 (6–32)
Month 9	26.13 (24.12)	18 (7–34.5)
Month 10	27.68 (27.36)	13 (7.75–41.5)
Month 11	23.88 (20.76)	12.5 (7.5–37.5)
Month 12	19.71 (19.59)	12 (5–31)

IQR, interquartile range; **NP**, nasal polyps; **SD**, standard deviation.

although Scangas et al. demonstrated advantages for surgery,³² they only analyzed dupilumab (and no other biologics, such as omalizumab), and no severe CRSwNP phenotypes or endotypes were included. Furthermore, it is known that up to 80% of patients experience recurrence despite functional endoscopic sinus surgery (FESS) or treatment with corticosteroids (intranasal or systemic) or doxycycline.^{2,33} Additional factors other than cost-effectiveness also need to be considered for surgery, such as the fact that multiple surgeries involve multiple recovery periods and repeated exposure to the potential negative effects of general anesthesia,³⁴ the increased risk of complications of primary and revision

FESS,³⁵ the patient's personal preferences,³⁶ and the indirect costs of surgery.³¹ In contrast, in real-world and randomized clinical studies, patients treated with omalizumab demonstrated reductions in CRS-related symptoms, endoscopic NP score and need for intranasal corticosteroids,^{13,16,37} showing improvements similar to those observed in patients receiving FESS.³⁷ Specifically, AERD patients, who are highly represented in our study, showed a good response to omalizumab both in CRSwNP and in asthma.^{13,27,38}

Two important conclusions can be drawn from our analysis. Firstly, omalizumab treatment was effective for NP size reduction over time, accompanied by improvements in clinical symptoms and QoL as reflected by the SNOT-22 questionnaire results. Secondly, SNOT-22 improvements were not explained by the changes observed in NP size or other variables, such as total IgE levels or eosinophilia. In this regard, we hypothesize that a decrease in nasal mucosa inflammation could explain this result. Additionally, this result reinforces the beneficial aspects of omalizumab in CRSwNP patients with mild asthma, regardless of the size of their polyps.

As mentioned, both polyp size and SNOT-22 improved significantly in our study, although SNOT-22 improvement was greater. This is a common observation in patients with recalcitrant nasal polyposis and AERD. However, our study focused on patients with mild asthma, in whom improvements in SNOT-22 due to asthma are unlikely. These results may possibly be explained by the measurements performed, as polyp size is an objective variable, while SNOT-22, a survey of patient symptoms, is a subjective variable. Previous studies have shown significant improvements in SNOT-

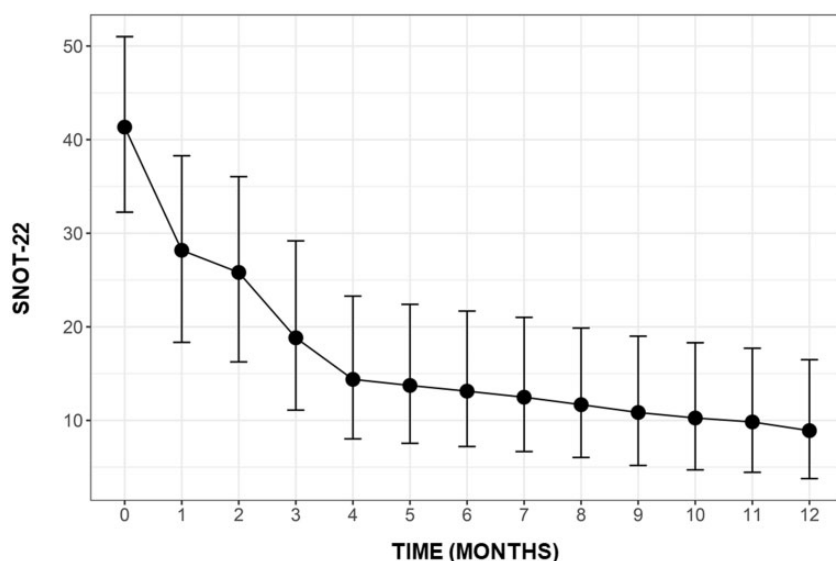


Figure 2. Patient quality of life measured by the SNOT-22 questionnaire over 12 months of omalizumab treatment.

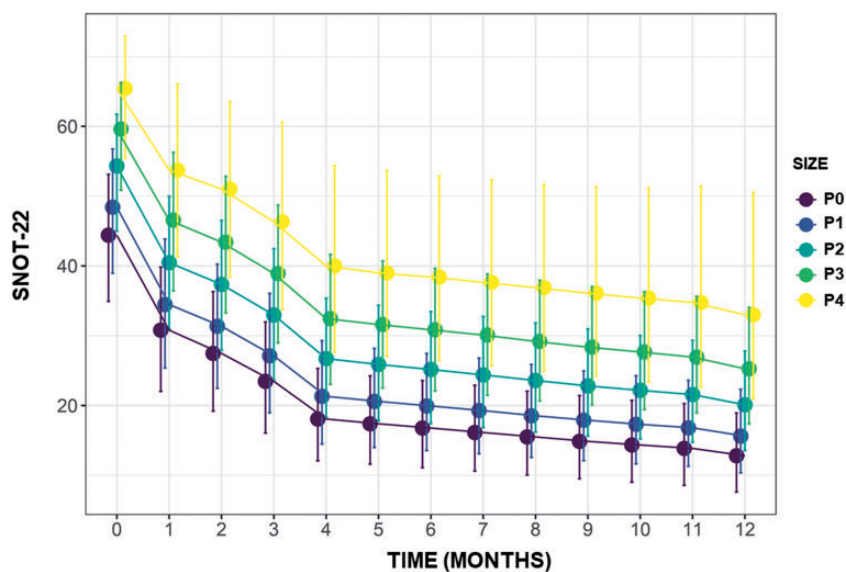


Figure 3. SNOT-22 evolution according to nasal polyp size over 12 months of omalizumab treatment.

22 in patients with CRSwNP treated with omalizumab,^{13,27} even when decreased urine levels of pathogenic mediators typical of AERD were detected.³⁸ Thus, it can be hypothesized that the decrease in inflammation in the submucosa may improve subjective patient symptoms in a manner not directly proportional to the decrease in polyp size. This fact would decisively affect patients affected by AERD.

Importantly, our analysis included 19 patients (82.61%) with AERD who also benefited from omalizumab therapy. So far, studies addressing the efficacy of this drug for the treatment of AERD have mainly focused on asthma outcomes.³⁹ Only a recent study by

Tiotiu *et al.* evaluates the effects of this biologic drug on nasal polyposis.⁴⁰ However, patients suffered from severe asthma, and results only evidenced improvements of this disease, but not NP size. The reason why omalizumab may be effective in these patients could reside in the pathophysiology of CRSwNP, which is characterized by prominent local production of IgE that may contribute to chronic inflammation by continuously activating mast cells.⁴¹ Although pathological AERD mechanisms have not yet been well established, several studies point to mast cell dysregulation as a major component in AERD.^{42–44} Thus, it has been suggested that ongoing signaling via mastocyte-associated IgE receptors permits

and amplifies activation responses to depletion of PGE₂. However, the nature of the antigens driving the IgE production remains unknown, although local production of antibodies against staphylococcal antigens and autoantigens have been reported in NP. In addition, the reduction of free IgE also decreases the expression and activation of high-affinity IgE receptors in mast cells.⁴³ The mechanism of action of omalizumab involves selective binding to free circulating IgE which decreases the expression of IgE receptors on mast cells, basophils and dendritic cells, and interferes with the activation of these effector cells,^{17,18} explaining its efficacy in patients with AERD. In fact, in a recent study published by Taniguchi et al., the authors support the efficacy of omalizumab as a mast cell stabilizer in patients with AERD, concluding that the current approach to treating intractable AERD is to use this monoclonal antibody, in addition to the drugs that the patient generally takes.⁴⁵ Additionally, it has been shown that omalizumab decreases urinary metabolites that are primarily derived from mast cells that secrete cysteinyl leukotrienes and PGD₂, both molecules involved in AERD.^{8,45,46} Several studies support the efficacy of this biologic in this set of patients more directly,^{47–49} demonstrating that the underlying mechanism of omalizumab is the suppression of PGD₂ and cysteinyl leukotriene overproduction, rather than the attenuation of eosinophilic inflammation.⁴⁷ The most recent evidence comes from a phase III clinical trial on the efficacy and safety of omalizumab in CRSwNP patients.⁴⁹ This study included 27.2% AERD patients who showed similar mean improvements in NP and nasal congestion scores at week 24 as patients without AERD.

This study also has some limitations. Firstly, because of its retrospective design, our results cannot be generalized, and should be interpreted with caution. Secondly, the lack of a control group may make the interpretation of results difficult. However, it is worth taking into account that all patients included in our study had chronic disease, with no changes or clinical improvements for years. Consequently, no changes in the progress of a putative control group were expected. Thirdly, this study did not assess the efficacy of omalizumab in comparison with other biologic therapies. As a result, a possible similar improvement upon treatment with other alternatives in these patients cannot be ruled out. Overall, the results are strong enough to support the efficacy of omalizumab in this scenario, paving the way for future observational studies.

Conclusion

In patients with recalcitrant CRSwNP and mild asthma, omalizumab treatment over 12 months improved NP size and patient QoL as evidenced by SNOT-22

questionnaire results, regardless of tissue eosinophilia and total IgE levels. Importantly, QoL improvements over time were independent of NP size, showing similar benefits for all patients analyzed. Consequently, omalizumab may be a therapeutic option for the treatment of CRSwNP patients and mild asthma.

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Miguel Armengot-Carceller, Noelia Muñoz-Fernández and Alfonso García-Piñero have participated in POLYP 1 (NCT03280550) and POLYP 2 (NCT03280537) clinical trials. The rest of the authors declare no conflict of interests.

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Supplemental Material

Supplemental material for this article is available online.

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Supplementary Table S1. Ordinal regression model to explore possible influence of time and other variables on nasal polyp size.

Variables	Odds ratio	95 % CI for odds ratio
Time (months)	0.613	[0.478, 0.735]
Total IgE (IU/mL)	0.998	[0.994, 1.002]
Age	1.076	[0.975, 1.194]
Eosinophilia	0.954	[0.706, 1.301]

CI, confidence interval

Supplementary Table S2. Ordinal regression model to explore possible influence of time and other variables on SNOT-22 scores.

Variables	Odds ratio	95 % CI for odds ratio
Time (months)	0.463	[0.369, 0.561]
Total IgE (IU/mL)	0.991	[0.981, 1.001]
Age	1.011	[0.734, 1.38]
Eosinophilia	1.441	[0.807, 2.709]

CI, confidence interval

Supplementary Table S3. Ordinal regression model to explore possible influence of nasal polyp size on SNOT-22 scores over time.

Variables	Odds ratio	95 % CI for odds ratio
Time (months)	0.613	[0.54, 0.68]
NP size	2.569	[1.671, 4.277]
Total IgE (IU/mL)	0.993	[0.986, 1]
Age	0.991	[0.856, 1.131]
NP size * Time	1.008	[0.966, 1.08]

NP, nasal polyps; **CI**, confidence interval