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

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Nasal polyposis (NP) is a subgroup of chronic rhinosinusitis (CRS). The overall prevalence is 1%-4%, and most cases are idiopathic [1]. Patients with CRS with NP (CRSwNP) comprise a heterogeneous group, of whom 30%-70% also have asthma [2]. These patients tend to have a more severe phenotype, a poor therapeutic response, and a high recurrence rate. Both CRSwNP and asthma negatively impact quality of life (QOL) and generate a considerable financial burden for society [2]. Omalizumab, a monoclonal antibody targeting the high-affinity receptor binding site on human IgE, was the first biologic drug indicated for the treatment of moderate-to-severe persistent allergic asthma. Interestingly, in patients with CRSwNP, the presence of asthma is associated with increased local IgE levels (itself associated with colonization by *Staphylococcus aureus* enterotoxins) [1] and severe eosinophilic inflammation [3], thus indicating a potential role for omalizumab in this context. In fact, some studies have already provided evidence on the efficacy of this drug for the treatment of CRSwNP [4-9], although more data are required [10]. The present manuscript describes a real-life study in which a series of patients with moderate-severe persistent allergic asthma and concomitant CRSwNP were treated with omalizumab for 12 months and prospectively followed up to assess changes in polyp size as the primary outcome measure.

We recruited 16 adult patients (49.6 [14.01] years). Asthma was diagnosed according to Spanish asthma guidelines (GEMA) [Supplementary reference 1], and CRSwNP was confirmed by nasal endoscopy and computed tomography (CT) scan when needed, following European guidelines (EPOS) [Supplementary reference 2]. All participants signed an informed consent form. The primary objective was to reduce the size of the polyps by administering omalizumab for 12 months. Polyp size was evaluated using the grading system proposed by Lildholdt [Supplementary reference 3] and recommended by the Polina Project [Supplementary reference 4]. The secondary objectives included CT scan of the sinuses (using the Lund-Mackay score), QOL (Rhinosinusitis Disability Index [RSDI] for CRSwNP, Mini Asthma Quality of Life Questionnaire [miniAQLQ] for asthma), severity of nasal problems (using a visual analog scale), evaluation of smell (using question 20 of the RSDI questionnaire), evaluation of asthma exacerbations (defined as per GEMA, obtained from medical records), evaluation of asthma control (Asthma Control Questionnaire [ACQ]), forced expiratory volume in the first second (FEV_1) (using spirometry), need for systemic corticosteroids (short-term courses of systemic corticosteroids during the previous 12 months and the 12 months of follow-up), and serum total IgE and eosinophil counts.

Patients were asked to keep a record of their symptoms according to the criteria established by the SEAIC-SEORL Consensus Document on Nasal Polyposis [Supplementary reference 4], as well as to keep a record of concomitant medication throughout the duration of the study. Data were analyzed using the Wilcoxon signed-rank test in order to assess possible changes in polyp size and other clinical parameters resulting from treatment. The influence of demographic/clinical characteristics (eg, sex, aspirin-exacerbated respiratory disease [AERD], previous surgeries) on reduction in polyp size was estimated using the Mann-Whitney test and the Spearman correlation coefficient. Potentially significant covariates ($P<.3$) were then included as main effects in a multiple regression model, with reduction in polyp size (difference between the initial and the final polyp size) as the dependent variable. *P* values less than .05 were considered significant. Results are expressed as median (IQR).

The study population comprised 16 adult patients (mean [SD] age, 49.6 [14.01] years, 9 females). Nine patients had AERD, and 7 had previously undergone endonasal sinus surgery (1 to 107 months before being included in the study, 1 patient had undergone 9 procedures). Patients had been diagnosed with asthma for a mean of 17 years [Supplementary reference 1]. The Table shows the main results after 12 months of treatment with omalizumab. Compared with baseline, a statistically significant reduction in polyp size measured by endoscopy was observed, with a median difference of 2.50 in the Lildholdt score ($P=.001$) (Supplementary figure 1). Similar results were confirmed in most patients when polyp size was evaluated using a CT scan of the sinuses, with a median difference of 1.50 in the Lund-Mackay score ($P=.011$), even though posttreatment scans were not available in 7 patients. When endoscopy findings were adjusted for sex, age, AERD, total IgE, and eosinophil count, no associations were found between these variables and the results. Although patients who had previously undergone surgery had higher

Table. Study Data Before and After Treatment With Omalizumab

Variables[a]	Pretreatment N=16	Posttreatment N=16	*P* Value
Polyp size (endoscopy)	4.00 (4.00-6.00)	1.50 (1.00-2.00)	.001
Sinus CT scan (Lund-Mackay score)[b]	16.5 (14.0-18.8)	15.0 (6.75-16.0)	.011
Quality of life			
RSDI	55.0 (42.0-76.0)	43.0 (6.0-45.0)	.01
Mini AQLQ	62.0 (37.0-75.0)	61.0 (47.5-92.5)	.136
VAS[c]	8.00 (5.50-10.0)	6.00 (3.00-9.50)	.089
Sense of smell[d]	2.50 (2.00-4.00)	2.00 (0.00-4.00)	.063
Asthma exacerbations (number)	5.00 (3.00-8.00)	0.00 (0.00-2.75)	.001
ACQ	14.0 (12.0-22.3)	12.0 (4.50-18.5)	.011
FEV_1, %	74.0 (59.3-82.8)	83.0 (69.3-94.5)	.026
Cycles of systemic corticosteroids	5.00 (3.00-8.00)	1.00 (0.00-1.75)	.001

Abbreviations: ACQ, Asthma Control Questionnaire; CT, computed tomography; FEV_1, forced expiratory volume in the first second; Mini AQLQ, Mini-Asthma Quality of Life Questionnaire; RSDI, Rhinosinusitis Disability Index; VAS, visual analog scale.
[a]Expressed as median (IQR).
[b]Pretreatment CT scan was performed in 14 patients; posttreatment CT scan was performed in 9 patients.
[c]VAS: Overall score of the degree of severity of nasal involvement.
[d]Improvements in sense of smell were quantified through the median scores obtained in RSDI question number 20.

values in the endoscopy prior to the intervention (*P*=.020), this characteristic was not associated with a greater or lesser improvement (*P*=.231). At the end of the study, we observed a reduction in the need for systemic corticosteroids, a significant improvement in the RSDI questionnaire score, a reduced number of exacerbations, better asthma control measured using the ACQ, and a significant improvement in FEV_1 compared with baseline. Although not statistically significant, a positive trend was also observed in the overall score for the degree of severity of nasal involvement (visual analog scale) and regarding the sense of smell. These results show that omalizumab is effective not only for the treatment of moderate-to-severe asthma, but also for reducing polyp size in CRSwNP patients, as evidenced by nasal endoscopy findings. This outcome was also confirmed by CT scan of the sinuses, although data were only available for 9 patients. While patients were treated according to the severity of their asthma, 13 of the 16 patients also met the criteria for biologic treatment in CRSwNP according to the recent recommendations of the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) [2]. New therapeutic alternatives are necessary, given the high burden of uncontrolled disease, the recurrence of NP after sinus surgery, and the adverse effects associated with repeated cycles of standard corticosteroid therapy [2]. In line with results obtained in allergic asthma patients reported elsewhere [Supplementary reference 5], we found that omalizumab improved asthma symptoms, the concomitant reduction in polyp size led to improved QOL, the need for systemic corticosteroids was reduced, and the sense of smell improved, although the results were not statistically significant, probably owing to the sample size. Our results are consistent with the 5 EUFOREA criteria established for defining response to biological treatment in CRSwNP patients [2], thus stressing the potential benefit of omalizumab in this context. Furthermore, our results confirm previous findings in CRSwNP patients with moderate-to-severe persistent allergic asthma, whose baseline characteristics were similar to those of our cohort [5-7, Supplementary references 6,7]. Given that omalizumab was selected under the approved indication for asthma, our findings may be subject to bias, since the response was only assessed for CRSwNP patients with allergic asthma and we cannot establish whether omalizumab would be as effective in nonallergic patients.

Our results should be interpreted with caution, given that we did not perform a randomized placebo-controlled clinical trial. The small sample size precludes a multivariate analysis to estimate the effect of other factors, such as previous surgery, disease severity, and serum IgE levels, which can modify the effect of omalizumab on the outcome of CRSwNP. In addition, the lack of specific information because of the real-life setting prevented us from ruling out topical nasal corticosteroids and their doses as potential confounders in the association between treatment with omalizumab and reduction in polyp size. However, consistent with previous results, our study shows a significant reduction in polyp size in patients with moderate-to-severe allergic asthma with concomitant CRSwNP treated with omalizumab over a long observational period of 1 year.

In conclusion, co-occurrence of NP and asthma symptoms constitutes a severe phenotype of CRSwNP that is often difficult to treat. Although further research is needed, our study shows that omalizumab can be effective in reducing NP size in patients with severe allergic asthma and concomitant CRSwNP.

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Conflicts of Interest

During the last 3 years J. Ruiz-Hornillos has received fees for talks from AstraZeneca, Chiesi, GlaxoSmithKline, Mundipharma, and Novartis. B. Rodríguez has received fees for talks from Mundipharma, AstraZeneca, and Chiesi. During recent years, A. Feliu has received fees for talks from GSK and AstraZeneca and for providing scientific consultancy services to ALK-Abelló. A. Moreno has received fees for talks from AstraZeneca and Chiesi. During the last 3 years, J. Domínguez-Ortega has received fees for scientific consultancy services and giving lectures and talks from AstraZeneca, Bial, Chiesi, GSK, Mundipharma, Novartis, Sanofi, and TEVA. M.J. Hernandez declares that she has no conflicts of interest.

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References

1. Stevens WW, Schleimer RP, Kern RC. Chronic Rhinosinusitis with Nasal Polyps. J Allergy Clin Immunol Pract. 2016;4:565-72.
2. Fokkens WJ, Lund V, Bachert C, Mullol J, Bjermer L, Bousquet J, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. Allergy. 2019;74:2312-9.
3. Van Zele T, Gevaert P, Watelet J-B, Claeys G, Holtappels G, Claeys C, et al. Staphylococcus aureus colonization and IgE antibody formation to enterotoxins is increased in nasal polyposis. J Allergy Clin Immunol. 2004;114:981-93.
4. Tiotiu A, Oster J, Roux P, Nguyen Thi P, Peiffer G, Bonniaud P, et al. Effectiveness of Omalizumab in Severe Allergic Asthma and Nasal Polyposis: A Real-Life Study. J Investig Allergol Clin Immunol. 2020;30:49-57.
5. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. J Allergy Clin Immunol. 2013;131:110-6.
6. Penn R, Mikula S. The Role of Anti-IgE Immunoglobulin Therapy in Nasal Polyposis: A Pilot Study. Am J Rhinolology. 2007;21:428-32.
7. Vennera M d. C, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. Thorax. 2011;66:824-5.
8. Bidder T, Sahota J, Rennie C, Lund VJ, Robinson DS, Kariyawasam HH. Omalizumab treats chronic rhinosinusitis with nasal polyps and asthma together-a real life study. Rhinology. 2018;56:42-5.
9. Guglielmo M, Gulotta C, Mancini F, Sacchi M, Tarantini F. Recalcitrant nasal polyposis: achievement of total remission following treatment with omalizumab. J Investig Allergol Clin Immunol. 2009;19:158-9.
10. Fokkens WJ, Lund VJ, Hopkins C, Hellings PW, Kern R, Reitsma S, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2020. Rhinology. 2020;0:1-464.

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