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 polyps (NP) are considered a subgroup of chronic rhinosinusitis which has an overall prevalence of 1-4%, most of the cases 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 immunoglobulin (Ig) E, was the first biologic therapy drug with indication 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 [1], (apparently induced by Staphylococcus aureus enterotoxins) 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]. This manuscript describes a real life study in which a series of patient with moderate-severe persistent allergic asthma, with concomitant chronic rhinosinusitis with nasal polyps, were treated with omalizumab during 12 months and prospectively follow up to assess changes in the size of nasal polyps as primary outcome.

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We recruited 16 adult patients (49.6 ± 14.01 years-old). Diagnosis of asthma was made according Spanish asthma guidelines (GEMA) [Sup ref 1] and chronic rhinosinusitis with nasal polyps confirmed by nasal endoscopy and CT scan when needed, following European guidelines (EPOS) [Sup ref 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 [Sup ref 3], recommended by Polina Project [Sup ref 4]. The secondary objectives included CT sinus scan (using the Lund Mackay score), quality of life (RSDI for CRSwNP, miniAQLQ for asthma), severity of nasal problem (using a visual analogue scale), smell evaluation (using question 20 of the RSDI questionnaire), asthma exacerbations (defined as in GEMA, obtained from medical records), asthma control (ACQ), Forced expiratory volume first second (FEV1) (from spirometry), need for systemic steroids (use of short term courses of systemic steroids during previous 12 months and in the 12 months follow up) and serum total Ig E and eosinophils 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 [sup ref 4], as well as to keep a record of concomitant medication throughout the duration of the study. In order to assess possible changes in polyp size and other clinical parameters due to treatment data was analyzed applying the Wilcoxon signed- rank test. On the other hand, the influence of demographic/clinical characteristics (eg, sex, aspirin-exacerbated respiratory disease [AERD], previous surgeries) on polyp size reduction was estimated with the Mann-Whitney U test and the Spearman correlation coefficient. Potentially significant ($p < 0.3$) covariates were then included as main effects in a multiple regression model, using as dependent variable the polyp size reduction

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(difference between the initial and the final polyp size) P -values less than 0.05 were considered significant. Results are expressed as median and interquartile range (IQR).

16 adult patients (49.6 ± 14.01 years [mean and standard deviation-SD-], 9 females) were included in the study. 9 patients suffer from aspirin-exacerbated respiratory disease and 7 were previously treated surgically with endonasal sinus surgery (ESS) (1 to 107 months before being included in the study, 1 patient operated till 9 ESSs). Asthma diagnosis last for a mean (SD) of 17 [Sup ref 1] years **Table 1** shows the main results after 12 months of treatment with omalizumab. A statistically significant reduction was observed in polyp size measured by endoscopy compared with baseline with a median difference of 2.50 Lildholdt scores (p = 0.001) (**Figure 1,** suppl). Similar results were confirmed in most patients when polyp size was evaluated using a sinus CT scan even though post-treatment scans were not available in 7 patients, with a median difference 1.50 Lund-MacKay scores p = 0.011;. 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 values in the endoscopy prior to the intervention (p = 0.020), this characteristic was not associated with a greater or/ lesser improvement (p = 0.231). At the end of the study, we observed a reduction in the need of systemic corticosteroids, a significant improvement in the RSDI questionnaire, a reduced number of exacerbations, a better asthma control measured by ACQ and a significant improvement in the forced expiratory volume (FEV1) compared to baseline. Although not statistically significant, a positive trend was also observed regarding overall score for the degree of severity of the nasal problem evaluation using a VAS and regarding the sense of smell. These results show that omalizumab is effective not only for the treatment of moderate severe asthma, but also for reducing polyp size in CRSwNP

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patients, as evidenced by nasal endoscopy findings. This outcome was also confirmed by sinus CT scan, although data were only available for 9 patients. Although the patients we report on were treated according to the severity of asthma 13 out of 16 patients could also met the criteria for biologic treatment in CRSwNP according to the recent European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) recommendations [2]. 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, new therapeutic alternatives are necessary [2]. In line with results obtained in allergic asthma patients reported elsewhere [Sup ref 5], we found that, omalizumab improved asthma symptoms, The concomitant reduction in polyp size led to improved QoL, a reduced need for systemic corticosteroids, and improvements in sense of smell, 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 also confirm previous findings in CRSwNP patients with moderate- severe persistent allergic asthma, whose baseline characteristics were similar to those of our cohort [5-7, Sup ref 6,7]. Because the election for omalizumab treatment was performed under the approved indication for asthma, we consider the bias could be that the response is only assessed for CRSwNP patients with allergic asthma and we cannot stablish if omalizumab would be as effective in not allergic patients.

Results in our study should be carefully evaluated taking into account that it is not a clinical trial using a placebo control group nor being randomized. Sample size is limited not allowing a multivariate analysis to estimate the effect of other factors as previous surgeries, severity of the disease, serum Ig E levels, that can modify the effect of

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omalizumab treatment on CRSwNP outcome. In addition, the lack of specific information because of its real-life setting, impaired discarding topical nasal steroids and their doses as potential confounders in the association observed between the treatment with omalizumab and the polyp size reduction. However, our study shows a significant reduction in polyp size in patients with moderate-severe allergic asthma with concomitant CRSwNP treated with omalizumab during a long observational period of one year, which is aligned with previous published results.

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

Conflicts of interest: In 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 the last years, A. Feliu has received fees for talks from GSK and AstraZeneca and scientific consultancy services from ALK-Abelló. A. Moreno has received fees for talks from AstraZeneca and Chiesi. M.J. Hernandez has no conflicts of interest. 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.

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Table. Pre- and post-omalizumab treatment measurements

Variables*	**Pre-treatment** ***N*** **= 16**	**Post-treatment** ***N*** **= 16**	***p*-value**
Polyp size (endoscopy)	4.00 (4.00-6.00)	1.50 (1.00-2.00)	**0.001**
Sinus CT scan (Lund-MacKay score)**	16.5 (14.0-18.8)	15.0 (6.75-16.0)	**0.011**
Quality of life			
RSDI	55.0 (42.0-76.0)	43.0 (6.0-45.0)	**0.01**
Mini AQLQ	62.0 (37.0-75.0)	61.0 (47.5-92.5)	0.136
VAS***	8.00 (5.50-10.0)	6.00 (3.00-9.50)	0.089
Sense of smell ****	2.50 (2.00-4.00)	2.00 (0.00-4.00)	0.063
Asthma exacerbations (number)	5.00 (3.00-8.00)	0.00 (0.00-2.75)	**0.001**
ACQ	14.0 (12.0-22.3)	12.0 (4.50-18.5)	**0.011**
FEV1 (%)	74.0 (59.3-82.8)	83.0 (69.3-94.5)	**0.026**
Cycles of systemic corticosteroids	5.00 (3.00-8.00)	1.00 (0.00-1.75)	**0.001**

*Expressed as median value and IQR

**Pre-treatment CT scan was performed in 14 patients; Post-treatment CT scan was performed in 9 patients

***VAS**, visual analog scale: Overall score of the degree of severity of your nasal problem

****Improvements in sense of smell were quantified through the median scores obtained in RSDI question number 20

CT, computed tomography**; RSDI**, Rhinosinusitis Disability Index; **Mini AQLQ**, Mini-Asthma Quality of Life Questionnaire; **ACQ**, Asthma Control Questionnaire; **FEV1**, forced expiratory volume in the firs second; **VAS**, visual analog scale

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