TÍTULO

EFFECTS OF BIOLOGIC THERAPY FOR CHRONIC RHINOSINUSITIS WITH NASAL POLYPS ON AIRFLOW AND NASAL RESISTANCE

PRELIMINARY RESULTS

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EFECTOS DE LA TERAPIA BIOLÓGICA SOBRE EL FLUJO AÉREO Y LA RESISTENCIA NASAL EN PACIENTES CON RINOSINUSITIS CRÓNICA CON PÓLIPOS

RESULTADOS PRELIMINARES

AUTORA

Xenia Iraisa Mota Rojas

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Tutor	Dr. D. Juan Maza Solano
Institución	Universidad Internacional de Andalucía
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Effects of biologic therapy for chronic rhinosinusitis with nasal polyps on airflow and nasal resistance: preliminary results.

Xenia Iraisa Mota Rojas

Advisor: Dr. Juan Maza Solano

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To Emma, for the stolen hours.

Abbreviations

AR	Acoustic rhinometry
CRSwNP	Chronic rhinosinusitis with nasal polyps
EAM	European agency of medications
ESS	Endoscopic sinus surgery
HPF	High power field
IL-4	Interleukin-4
IL-13	Interlekuin-13
IL-5	Interleukin-5
NAF	Nasal airflow
NAO	Nasal obstruction
NOSE	Nasal obstruction symptom evaluation
Pa	Pascal
PEF	Pulmonary expiratory flow
PNIF	Peak nasal inspiratory flow
PROM	Patient reported outcome measures
QoL	Quality of life
RM	Rhinomanometry
SNOT-22	Sinonasal outcome symptoms test 22
SSIT	Sniffin´Sticks identification test
VAS	Visual analog scale

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SUMMARY

Main objective: to assess the effect of monoclonal antibodies on nasal airflow in patients with chronic rhinosinusitis with nasal polyposis, with or without associated endoscopic sinus surgery during treatment.

Design: Prospective cohort study.

Setting: secondary care hospital.

Participants: patients suffering from severe chronic rhinosinusitis with nasal polyps and comorbid severe asthma staring treatment with a monoclonal antibody.

Outcomes measure: active anterior rhinometry was performed at baseline, and during treatment at weeks 16, 24 and 52. Also, after endoscopic sinus surgery, if performed.

Conclusions: a correlation between PRO to each other but could not demonstrate a significant correlation between nasal airflow and quality of life in patients with CRSwNP. Also, we found a correlation between left and right nasal airflow, but not that biological treatment improves the nasal airflow and resistance in those under treatment. However, the updated guidelines recommend that the first evaluation should be done on week 24 instead of week 16.

INTRODUCTION

Nasal obstruction (NAO) is the most prevalent symptom in nasal diseases[1,2], including chronic rhinosinusitis with nasal polyps (CRSwNP); and it is well known that turbulent airflow facilitates mixing the airflow with the nasal mucosa and ensures maximal air conditioning, with efficient warming and humidification of the air as it passes through the nose to the lungs[3,4].

In patients with CRSwNP subjective evaluation of nasal obstruction is made using the visual analog scale or validated quality of life questionnaires like the sinonasal outcomes test 22 (SNOT22)[5] or the nasal obstruction symptom evaluation (NOSE)[1], while the degree of obstruction and inflammation can be visually assessed through nasal endoscopy using the modified Lund-Kennedy scale[6].

The size of the nasal polyps correlates well with subjective nasal obstruction but does not predict the severity of other symptoms[5,7], therefore nasal obstruction should be objectively evaluated by measuring the nasal airway using either acoustic rhinometry (AR), peak nasal inspiratory flow (PNIF)[8,9] or rhinomanometry (RM). Rhinomanometry is a useful tool to measure NAO caused by any pathological factor[10] and an acceptable correlation between anterior active RM has been reported previously, both in healthy and obstructed noses[1]. Contrary to peak nasal inspiratory flow [that correlates with the pulmonary expiratory flow (PEF)[2], rhinomanometry is not influenced by patient´s pulmonary function. Nevertheless, a lack of reliable correlation between subjective and objective measurements of nasal obstruction has been reported[10–12].

On the other hand, CRSwNP involves inflammation of the nasal mucosa, eosinophil infiltration, local IgE formation, and cytokine production[5,9,13,14], leading to inadequate nasal breathing and other symptoms that negatively impact the quality of life (QoL)[13].

Traditionally CRSwNP treatment has involved nasal irrigations, nasal corticosteroids, systemic corticosteroids, and surgery[9,15,16], but currently,

biologics agents offer a new therapeutic option for patients with uncontrolled CRSwNP[9,14,15]. They represent a great hope for achieving good control of this disease, with or without associated asthma[13]. These medications are mainly used when both pharmacological therapy and surgery do not provide adequate symptom control.

Currently, the European Agency of Medications (EAM) has approved three monoclonal antibodies for the treatment of CRSwNP: Dupilumab, Omalizumab, and Mepolizumab. The criteria for initiation of these monoclonal antibodies have been previously specified elsewhere[9,14,15,17]

Dupilumab is a fully human monoclonal antibody that binds to the alpha subunit of interleukin-4 receptors to inhibit interleukin- 4 (IL-4) and interleukin-13 (IL-13) signaling. It has been accepted for the treatment of CRSwNP by the United States Food and Drug Administration (FDA) and the European Medicines Agency (EMA) in 2019.

On the other hand, the therapeutic target of Omalizumab is IgE. This monoclonal antibody reduces both tissular and serum IgE, thus blocking the IgE-mediated inflammatory cascade[18]. It was approved by both the FDA and EMA in 2020 to treat CRSwNP, although it has been used for severe asthma since 2005.

While Mepolizumab is a humanized monoclonal antibody that blocks the alpha subunit of the interleukin-5 (IL-5) receptor on the eosinophil, indicated as add-on intranasal corticosteroid therapy for the treatment of adults with severe CRSwNP for whom systemic corticosteroid therapy and/or surgery do not provide adequate disease control. It is indicated as a long-term treatment.

Lastly, Benralizumab, a monoclonal antibody that blocks the alpha receptor of IL-5, and activates the FcγRIIIa of natural killer cell, macrophages and neutrophils is currently under clinical trial for CRSwNP. It is approved for severe asthma.

Unfortunately, the high costs of these medications, the risk of anaphylaxis, and the use of subcutaneous or intravenous injection are limiting factors in their widespread application[5].

Objectives

To analyze the effect on nasal airflow of monoclonal antibodies used for the treatment of chronic rhinosinusitis with polyps; to accurately document and report, in a standardized fashion, patient's response to biologic therapy. We opted for rhinomanometry as patients included in this study have severe asthma.

METHODS

A prospective cohort study according to the STROBE guideline on patients starting treatment with a monoclonal antibody from severe CRSwNP, from February 2022 to June 2023, on a secondary care hospital. This study was approved by the Institutional Review Ethics Board, code 2314.

Participants

Patients who met the following criteria were included: severe uncontrolled asthma with comorbid severe uncontrolled CRSwNP; as the main indication for treatment was asthma, but patients suffering from CRSwNP were selected for indirect evaluation of this pathology. Also, health-related quality of life issues, and previous sinus surgery. Before enrollment, all patients with severe chronic rhinosinusitis and asthma were evaluated by the hospital airway committee for the initiation of biologic treatment. All patients signed informed consent to participate in this study.

Patients under 18 years-old, and pregnant women were excluded.

Disease extension

Patients were evaluated at base line, and at weeks 16, 24, and 52. Their symptoms were recorded using the Sinonasal Outcome Test-22 (SNOT-22, range 0 to 110, lower = better) and the Nasal Obstruction Scale (NOSE, 0 to 25,

lower= better). The extent of disease was assessed using the modified Lund-Kennedy endoscopic score (0 to 12, higher = worse), Meltzer polyp score, and the Lund-Mackay computerized tomography (CT) score (0 to 24, higher = worse), this one at base line and at week 48. The Sniffin´stick identification test (SSIT) (0 to 12, higher= better) was used for olfaction evaluation. Septal deviation was classified according to the Mladina classification[19], and its severity was assessed using two levels of severity; while turbinated hypertrophy degree was scored according to Camacho classification[20]. Nasal airflow and resistance were measured by active anterior rhinomanometry (NR6, GM, UK) as recommended by the Committee Report on Standardization of Rhinomanometry[21], sampling pressures for unilateral measures at 75 and 150 Pascal (Pa), using an adult standard Bi-Mask P/NR6.

Surgery criteria

Surgery was performed if at week 16 patients presented the criteria indicated by Rudmik et al.: 8 weeks of intranasal corticosteroids and/or a single course of systemic corticosteroids (1-3 weeks), Lund-Mackay ≥1, and SNOTT 22 > 20 after treatment.

Statistical analysis

Statistical analysis was performed using the SPSS software, version 23 for Mac (IBM Corporation, Chicago, Il.). Spearman´s Rank-Order Correlation was used to analyze the quantitative variables, Mann-Whitney test and Wilcoxon signed-test. A p-value of <0.05 was considered statistically significant. As septal deviation and inferior turbinated hypertrophy also cause nasal obstruction, therefore act as mediators, a stratified analysis was use to asses this.

RESULTS

A total of 10 patients were included (7 females and 3 males) in the period studied. Median age was 55,5 years (range 42-80). 5 (50%) patients started treatment with Mepolizumab, 3 (30%) patients with Dupilumab, and 2 (20%) patients with Benralizumab. Benralizumab, although not approved for CRSwNP but for severe

asthma, was started in two cases: Case 5 because the patient recently finished treatment for breast cancer and rather longer intervals between doses; and in Case 6 started because of good control of her CRSwNP. No patients was given Omalizumab. Demographic and baseline data are summarized in table 1.

Table 1. Demographic and baseline data.

Features	**Overall** n (%)
Sex	
Male	3 (30)
Female	7 (70)
Age, median (IQR)	55.5 (42;80)
Asthma,	10 (100)
Aspirin exacerbated respiratory disease (AERD)	5 (50)
Eosinophils	500 (100;1100)
Endoscopic sinus surgery, yes	9 (90)
Endoscopic sinus surgery, median (IQR)	1 (1; 3)
Nasal endoscopic score, median (IQR)	5 (3;7)
Lund-Kennedy score, median (IQR)	9 (7;10)
Lund-Mackay score, median (IQR)	19 (10;24)
Olfaction, Sniffin´stick median	5 (4;7)
Septoplasty, yes	2 (20)
Septal deviation.	9 (90)

All patients, except case 5, have undergone previous endoscopic sinus surgery (ESS), and two patients have also undergone septoplasty. However, a septal deviation was observed in 9 patients, and all of them also presented a grade 1 inferior turbinal hypertrophy, but the stratified analysis of septal deviation related

to nasal airflow showed no statistically significant difference at baseline and week 16 (figure 1).

On the same vein, no relationship were found regarding airflow and the nasal polyp score (NPS), the Lund-Kennedy score and the Lund-Mackay score at baseline.

Both SNOT22 and NOSE were used as patient-derived measurements for quality-of-life during each visit. At baseline and at week 16 these quality-of-life measures were related to each other, p=0.023 and p=0.014 respectively, but not to airflow. Nevertheless, left and right nasal airflow (NAF) measures were related to each other at baseline, p=0.010. No statistically significant difference was found between the nasal airflow at baseline and at week 16, but the statistical power was merely 0.2411 because of the small sample size. A sample of at least 50 individuals is needed to reach a power of 0.80. No further correlation were studied because only haft the same had reached advanced stages. The median score at baseline and weeks 16, 24, and 52 are summarized in table 2A and 2B.

Table 2A. Summary of quality-of-life and objectives outcomes measures.

Variables	**Baseline Median (IQR)**	**Week 16**	**p Value**
SNOT22	48 (8;99)	41 (29;55)	0,441
NOSE	70 (0;100)	35 (25;46)	0,092
Left nasal airflow	66,3 (7;550)	334 (161;431)	0,327
Right nasal airflow	131,6 (78;495)	176 (51, 324)	0,889
Olfaction	5 (4;7)	7 (3;8)	0,410
Lund-Kennedy	9 (7;10)	8 (3;11)	0,307
Nasal polyps Score	5 (3;7)	5 (3;7)	1,000

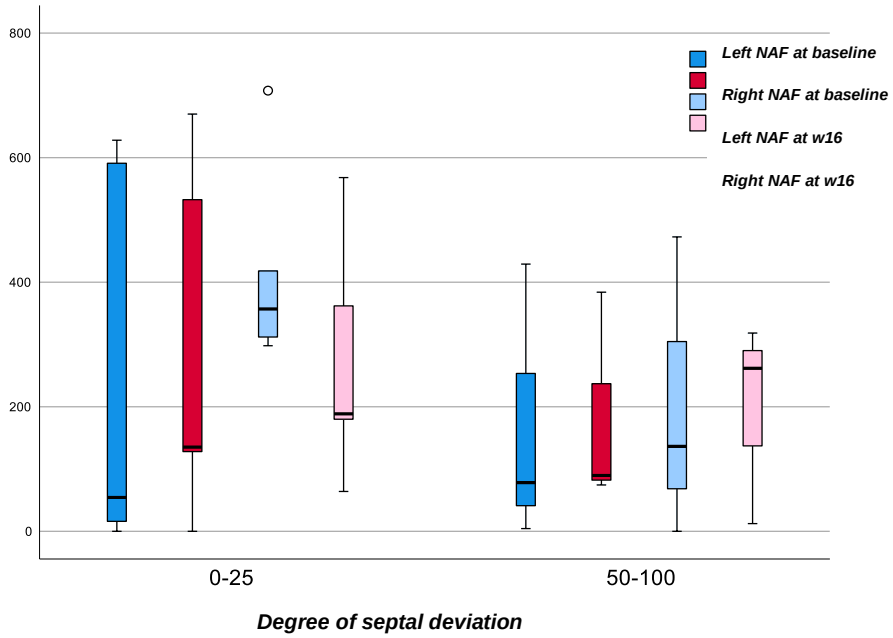
No further correlation were studied because only 4 patients reached week 24 and only 2 patients are past week 48.

Table 2B. Summary of quality-of-life and objectives outcomes measures on the sample.

	Baseline	**week 16**	**week 24**	**week 52**
	Median (IQR)	***Median (IQR)***	***Median (IQR)***	***Median (IQR)***
SNOT22	48 (8;99)	41 (29;55)	46 (38;84)	36 (33;)
NOSE	70 (0;100)	35 (25;46)	67 (38;96)	27 (10;)
Left nasal airflow	66,3 (7;550)	334 (161;431)	170 (40; 470)	343 (325;)
Right nasal airflow	131,6 (78;495)	176 (51, 324)	108 (12; 255)	357 (192;)
Olfaction.	5 (4;7)	7 (3;8)	3 (0;6)	6 (6;)
Lund-Kennedy	9 (7;10)	8 (3;11)	6 (3;9)	5 (4;)
Nasal polyps score	5 (3;7)	5 (3;7)	5 (2;6)	3 (2;)

No statistical test were run on weeks 24 and 52 because of the small number of patients at those stages.

Figure 1



Nasal airflow at baseline and at week 16 related to the degree of septal deviation. No statistically significant difference was found between groups.

Figure 2. *Left nasal airflow related to monoclonal antibodies.*

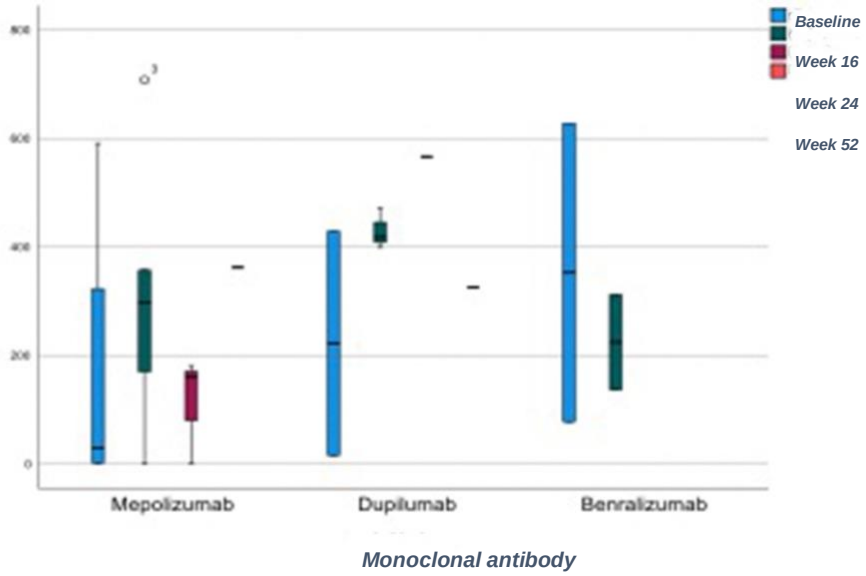
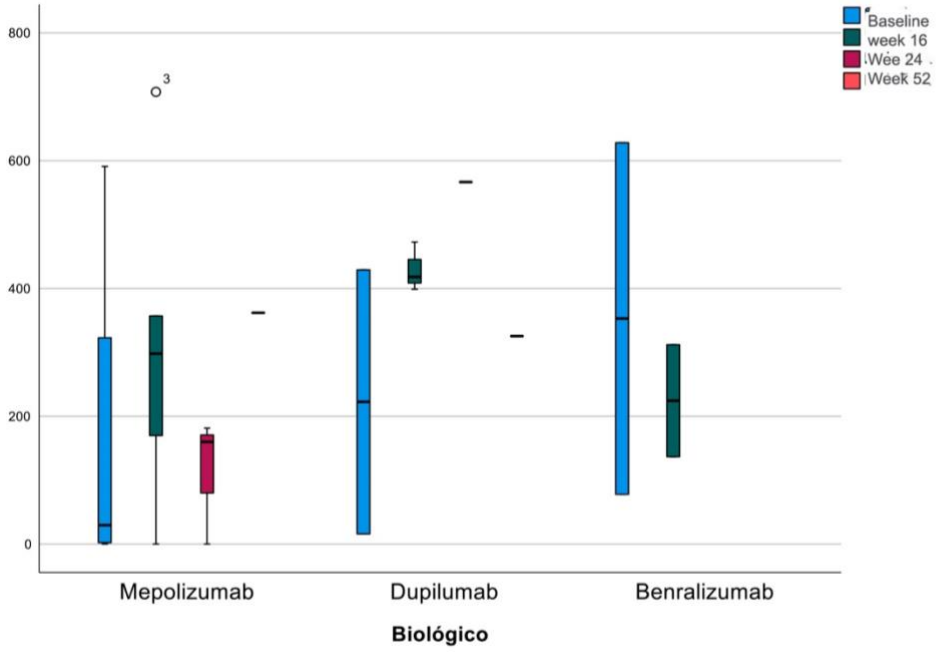


Figure 3. Right nasal airflow related to monoclonal antibodies



In patients with severe nasal obstruction, it was not possible to obtain any resistance measurements using the anterior rhinomanometry, as some degree of nasal passage must be patent for unilateral measurements of pressure and flow. Nevertheless, graphics were obtained and are shown here. This was the situation of Case 3 at baseline (Fig.4), and of Case 4 at week 16 (Fig.5).

Figures 4 show rhinomanometry of Case 3.

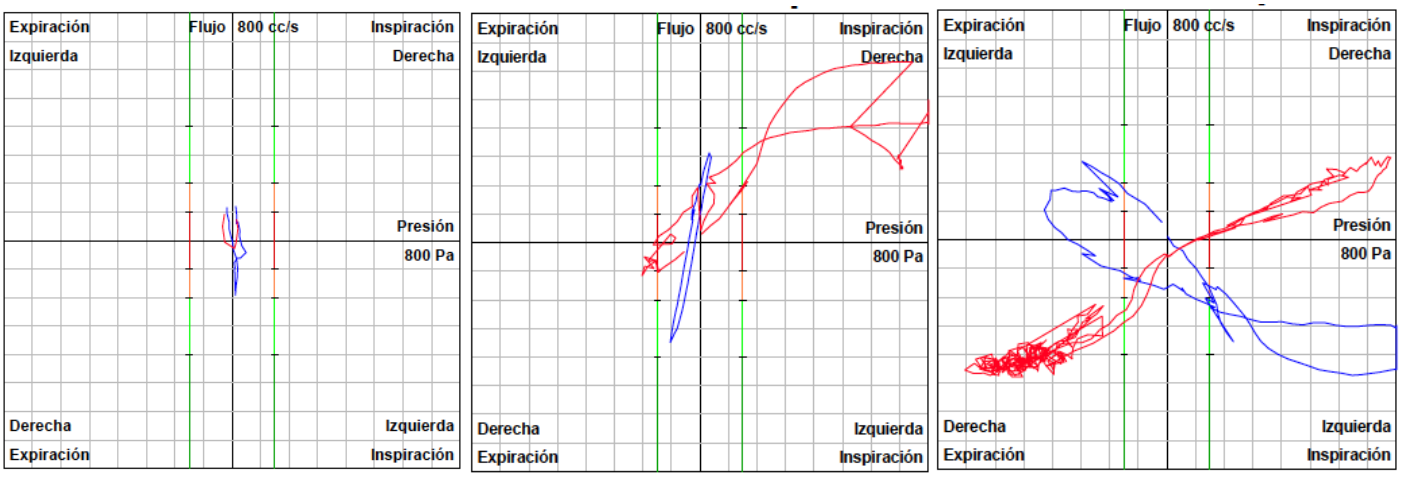


Fig. 4A shows Case 3 at baseline with minimal airflow, unable to achieve neither 75 or 150 Pa. Fig. 4B and 4C show rhinomanometry at week 16 and 24 on Mepolizumab show improves on both airflow and pressure, respectively.

Figures 5 show rhinomanometries of Case 4.

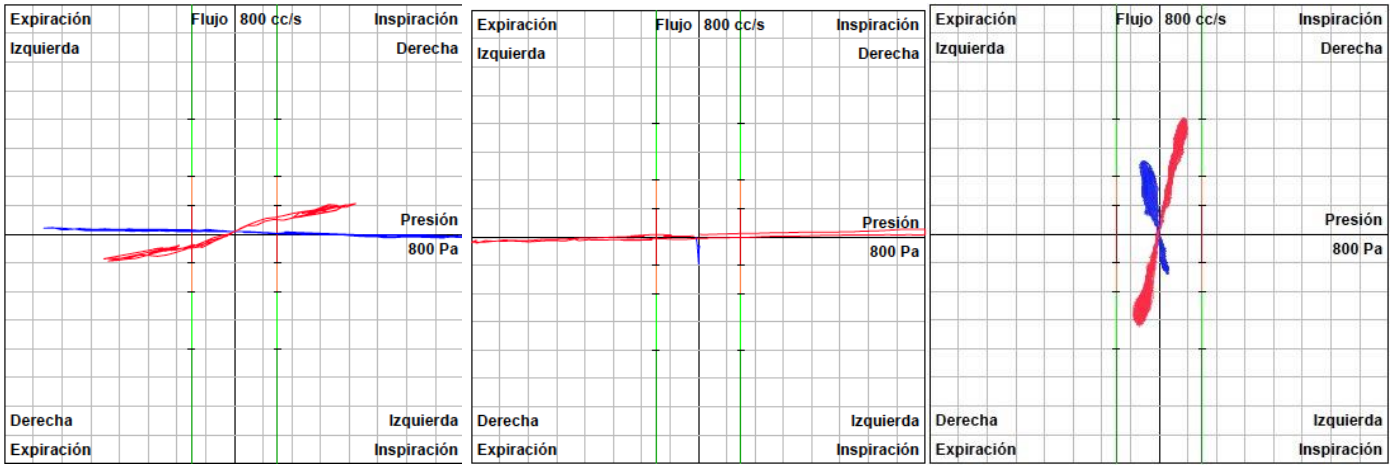


Figure 5A baseline, 5B week 16 on Mepolizumab, and 5C at week 24 on Mepolizumab, after a full-house FEES.

Surgery

Two patients (Cases 3 and 4) required endoscopic nasal surgery during the treatment period (one actual surgery was performed and the other one was planned). Both on Mepolizumab. Surgery consisted of polypectomy, infundibulotomy, middle meatal antrostomy, opening of the frontal recess through a Draf I, opening the bulla, all the anterior, basal lamella, posterior ethmoidal cells and sphenoid sinus, and removal of the ethmoidal mucosa. No complications were reported during or after surgery. Follow up after surgery was made every two weeks for 6 weeks, and then as indicated for the biologic treatment.

Other treatments

Case 4 also underwent a long course of Doxycycline 5 weeks after surgery because of the fast worsening of her symptoms and endoscopic findings. As this failed to demonstrate improvement for the patient, the monoclonal antibody has been changed.

Side effects

No side effects were reported.

DISCUSSION

Although the subjective feeling of nasal congestion is related to patient´s quality of life, it could be affected by the patient´s phycological status[10]. Therefore, objective measures are performed[15].

Active anterior rhinomanometry is the most commonly used method of rhinomanometry. Tompos et al[10] demonstrated that active anterior rhinomanometry is an appropriate diagnostic tool to determine the obstruction caused by nasal pathological factors. When using it, results must be reported with the 150 Pa reference pressure. Nevertheless, if the pressure level of 150 Pa cannot be reached, the lower nasal pressures of 75 and 100 Pa should be displayed. However, in patients with complete obstruction of the nasal cavity it is

not possible to obtain any resistance measurements using anterior rhinomanometry, as some degree of nasal passage must be patent for unilateral quantification of pressure and flow.

Another authors have reported reduced nasal airflow in individuals with CRSwNP through the use of PNIF measurements[2]. However, it is important to note that this particular study excluded patients with severe pulmonary dysfunction, which is known to be correlated with PNIF and acts as a potential mediator. It should be acknowledged that in Spain, the Ministry of Health currently provides financial coverage for monoclonal antibody therapy exclusively for patients with severe asthma, regardless of the presence of CRSwNP. Consequently, the assessment of pulmonary function and its impact on nasal airflow cannot be disregarded, particularly considering that a significant number of individuals undergoing this treatment exhibit compromised pulmonary function.

On the same vein, another study by Ottaviano et al[22]. on nasal patency, quantified by PNIF, of patients with CRSwNP treated with Dupilumab did not find correlations between nasal symptoms and airflow at baseline, but further evaluations during follow-up did show differences. However, patients with asthma were not included.

On the other hand, the impact on QoL in chronic disease like CRSwNP has been stated previously[9,13,15], as the role of monoclonal antibodies in improving PROMS. A Cochrane review of biologic agents for CRSwNP concludes that after 24 weeks of treatment, patients on Dupilumab have a better quality of life than those who were not and that their polyps reduced[23], but could make conclusions of patients under Mepolizumab and Omalizumab. However, in a study by Bachert et al[24]. improvement of QoL in patients with CRSwNP on Mepolizumab was found using the 36-item short-form (SF-36). Nevertheless, no specific nasal symptoms were assessed in this study.

Finally, patients undergo surgical treatment aimed at reducing symptoms and improve their quality of life. Although adverse effects on nasal-air conditioning have been observed with radical sinus surgery[4]. Currently, previous ESS is a

criterion for biologic treatment, because of the improvement on delivery of topical medication afterwards and the high cost of monoclonal antibodies. Nevertheless, not all patients want to undergone recurrent surgeries. In those that respond well to biologics, surgical intervention may be avoided. If biologics successfully reduce inflammation and the size of nasal polyps, this should also be visible using endoscopy and computerized tomography (CT) scans. These changes can be documented and quantified using the relevant scoring system.

CONCLUSION

This study of nasal airflow and resistance, and health-related quality of life in patients with CRSwNP had a preliminary analysis at week 16 for reasons inherent to this master´s thesis; and as stated at the EPOS2020.

We found a correlation between PROMs to each other but could not demonstrate a significant correlation between nasal airflow and quality of life in patients with CRSwNP. Also, we found a correlation between left and right nasal airflow, but not that biological treatment improves the nasal airflow and resistance in those under treatment. However, the updated guidelines recommend that the first evaluation should be done on week 24 instead of week 16.

The main limitation of this study is its small sample size. This is the reality of small, secondary care hospitals. Bigger studies and studies with long-term data on this subject are needed. A possible way to achieve this is by performing multicentric studies, using a main-common database.

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Firma:

Email: