Clinical evaluation protocol for chronic rhinosinusitis with polyposis during treatment with biological agents

Original Article

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Abstract

Introduction: Chronic rhinosinusitis with nasal polyposis is a common pathology in Otorhinolaryngology, and the available therapeutic options are medical and/or surgical. Medical therapeutic options, in addition to topical and oral corticosteroid therapy, include biological agents. Three biological agents were recently approved for the treatment of chronic rhinosinusitis with nasal polyposis in Portugal, and are indicated in critically ill patients in whom the disease is not controlled with topical nasal corticosteroid therapy, and in whom surgery (unless contraindicated) and/or systemic corticosteroid therapy did not provide adequate control of the disease.

Objectives: To propose a clinical evaluation protocol for patients undergoing biological treatment.

Methods: A review of the relevant medical literature was performed, namely from the two main international working groups on this topic: European Position Paper on Rhinosinusitis and Nasal Polyps 2020 (EPOS) and European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA).

Results: The proposed protocol can be divided into three phases: an initial phase involving collection of demographic and clinical data, a second phase for evaluation of patient eligibility for biologicals based on well-defined admission criteria, and a third phase with a proposal for follow-up and application of treatment efficacy and discontinuation criteria.

Conclusion: This clinical protocol presents a proposition for the uniform collection of standardized data to be used in clinical practice and for conducting prospective and/or retrospective multicenter studies, along with a proposition for follow-up and evaluation of efficacy/failure of treatment with biological agents in patients with chronic rhinosinusitis with polyposis.

Keywords: Chronic rhinosinusitis with polyposis, Biological Agents, Clinical Protocol

Introduction

Definition

Chronic rhinosinusitis (CRS) is a syndrome characterized by symptomatic sinonasal inflammation persisting for more than 12 weeks. In adults, it is clinically defined by the presence of two or more of the following symptoms:

- Nasal obstruction and/or anterior/posterior rhinorrhea (at least one of these two symptoms is mandatory) and
- Pain/facial pressure and/or hyposmia/anosmia.

This is a broad definition and does not specify the etiology, pathogenesis, and natural history of the disease. In a small subset of patients, this syndrome occurs in association with other systemic disorders or local processes (secondary rhinosinusitis). In the vast majority of cases the etiology is unknown (primary rhinosinusitis), although various environmental and genetic/epigenetic factors have been proposed. Genetic and epigenetic variation of the immune response is believed to play a key role[1]. Most environmental etiologic factors remain unknown, but tobacco, fungi, viruses, bacteria, pollution, and allergens have been implicated. The most commonly associated microbiological agent is Staphylococcus aureus , but some studies have also implicated nasal microbial community dysbiosis as an etiological factor[2-9].

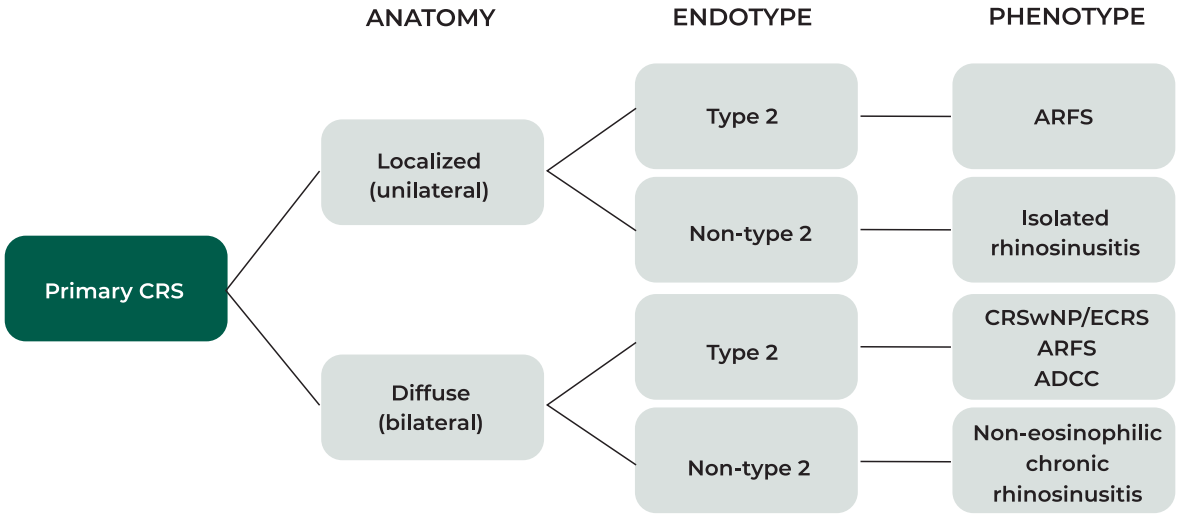
Environmental and individual factors interact with each other and trigger one or more chronic inflammation pathways (endotypes) that lead to the clinical presentation (phenotype).

Pathophysiology

The sinonasal mucosa serves as a barrier that limits and regulates the interaction between environmental factors and the immune system[10].

In healthy people, when this barrier is crossed, a self-limited and specific (cellular and humoral) immune response is generated, which targets pathogens. Type 1 immune response targets viruses, type 2 parasites, and type 3 immune response targets extracellular bacteria and fungi. In the case of CRS, this mucosal invasion results in a chronic inflammatory response that uses type 1, 2, or 3 inflammatory pathways alone or in combination. As mentioned above, there is no evidence of a specific dominant microbiological agent and the immune response is usually polyclonal, against antigens from several organisms, including the nasal microbiota[11,12]. In some cases, the body's antigens are also targeted by the immune

Figure 1
Classification of primary chronic rhinosinusitis according to the the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020.



ARFS: Allergic fungal rhinosinusitis; ADCC: Atopic disease of the central compartment; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyps; ECRS: Eosinophilic chronic rhinosinusitis.

response, but this is seen as a phenomenon secondary to chronic inflammation[13].

In type 1 immune response, the cytokines interferon (IFN)-gamma and interleukin (IL)-12 are produced in response to viral antigens; in type 3 immune response, the cytokines are IL-17A and IL-22 (which target extracellular bacteria and fungi).

The cytokines produced in the type 2 immune response are IL-4, IL-5, and IL-13. They are important in immunity against parasites and regulate tissue regeneration after injury; they promote an IgE-mediated inflammatory response. The type 2 immune response, formerly called T helper type 2 inflammation, is driven by inflammatory mediators produced by Th2 lymphocytes, such as cytokines IL-4, IL-5, IL-9, and IL-13. In this immune response, eosinophils play the main role at the cellular level. An elevation of local IgE level is also evident, both in the tissues and serum. With the later identification of other non-Th2 cells capable of producing the same cytokine profile (such as type 2 innate lymphoid cells), the inflammation came to be referred to as type 2 immune response. IL-5 is an important cytokine in the differentiation and maturation of eosinophils at the medullary level. In addition, it is an activator of eosinophils and increases their survival in tissues, thereby reducing the degree of apoptosis. IL-4 leads to the differentiation of T lymphocytes into Th2, induces IgE production by B lymphocytes, plays a role in chemotaxis of eosinophils, and leads to the recruitment and activation of mast cells and basophils. IL-13 is chemotactic for eosinophils, induces B lymphocytes to produce IgE, and activates mast cells and basophils. In addition, it promotes mucus secretion, goblet cell hyperplasia, and collagen production. IL-33 is also a mediator of type 2 inflammation. It binds to the surface receptors on Th2 lymphocytes, innate lymphoid cells, basophils, eosinophils, mast cells, and dendritic cells, thus activating inflammation in the airways. Direct exposure to Staphylococcus aureus at the airway mucosal level appears to increase the expression of IL-33, which promotes the production of cytokines such as IL-5 and IL-13, which in turn play a key role in the initiation and/or maintenance of type 2 inflammation in CRS with polyposis[14]. CRS with type 2 immune response is most commonly associated with asthma and resistance to treatment with topical corticosteroids. It may also be associated with respiratory disease exacerbated by nonsteroidal anti-inflammatory drugs. Tissue inflammation is often associated with remodeling patterns (fibrosis), polyposis, and fibrin deposition. In addition to asthma, the other comorbidities commonly present in patients with CRS with polyposis are atopic eczema, hives, nodular prurigo, and eosinophilic esophagitis. It is generally agreed that in CRS, mucosal invasion activates the type 1, 2, and 3 immune responses; however, in CRS this response is polyclonal rather than a specific and targeted monoclonal (physiological) response[11,12].

Treatment

In cases of bilateral chronic diffuse rhinosinusitis, regardless of having the type 2 endotype or not, the basic treatment includes topical corticosteroids and nasal lavage with saline[1]. In addition to pharmacological treatment, exposure to factors that cause worsening of the disease, such as tobacco and pollution, should be avoided. International recommendations differ widely regarding the use of antibiotics and oral corticosteroids as the initial pharmacological treatment. In cases in which initial pharmacological treatment is insufficient, further investigation with computed tomography (CT) of the paranasal sinuses and endotype evaluation ("type 2" or "non type 2") is indicated. Patients with type 2 endotype (tissue eosinophilia ≥ 10 eosinophils/high-power field or peripheral eosinophilia ≥ 250 or total IgE ≥ 100) tend to be more resistant to pharmacological therapy and have a higher post-surgical recurrence rate[1].

There is considerable controversy regarding the most appropriate time for surgery in CRS. In a recent study[15] in adults with uncomplicated CRS, it was concluded that endoscopic sinus

surgery (ESS) should be considered in patients with CRS with:

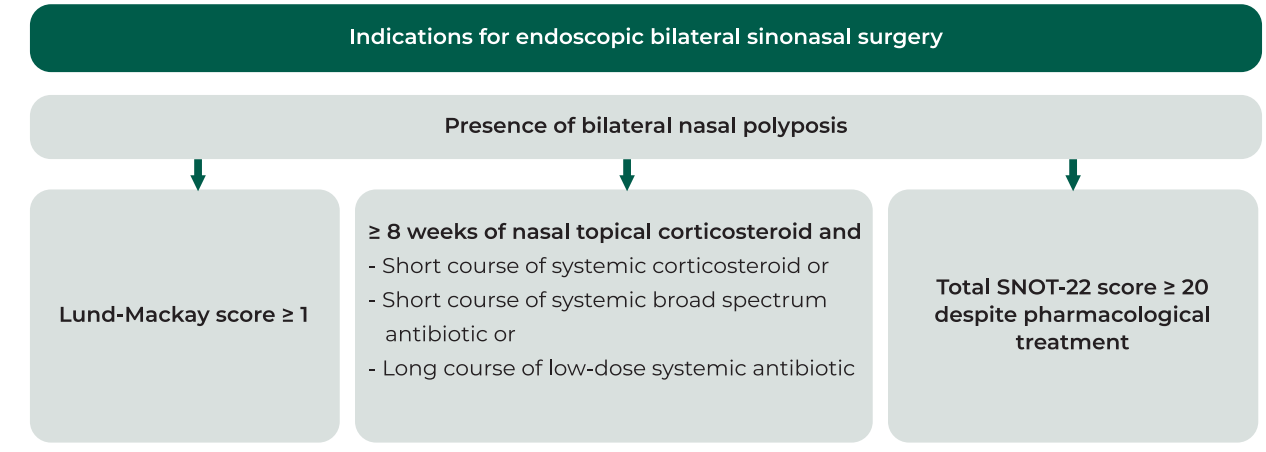
- Lund-Mackay score ≥ 1 and
- At least eight weeks of treatment with nasal topical corticosteroid and
  - Short course of systemic corticosteroid or
  - Short course of systemic broad-spectrum antibiotic after culture or
  - Long course of a low-dose systemic antibiotic with anti-inflammatory action.
- Total SNOT-22 score ≥ 20 despite pharmacological treatment.

It should be emphasized that CRS is a chronic disease and that ESS is a therapeutic modality that aims to create the ideal anatomic conditions for topical corticosteroids to act. According to the literature, in chronic type-2 bilateral diffuse rhinosinusitis, the surgical approach may vary from simple polypectomy (removal of polyps from the nasal cavity) to the opening of the paranasal sinuses (maxillary approach and complete frontosphenoethmoidectomy), often called "full-house FESS". Another type of surgical approach (more aggressive) includes the removal of the entire sinus mucosa (reboot surgery). The choice of the type of surgical approach depends on the surgeon's preference; however, the efficacy in terms of recurrence is generally higher for more aggressive procedures[16-18].

Continuous topical treatment is mandatory after surgery. If surgery combined with optimized pharmacological treatment fails, an alternative treatment should be considered, namely the use of biologic agents (monoclonal antibodies). Three biologic drugs are currently available in Portugal for different diseases with type 2 inflammation: anti-immunoglobulin E (IgE): omalizumab; anti-IL-5/IL-5 receptor (IL-5R): mepolizumab; and anti-interleukin 4 receptor (IL4R): dupilumab. Dupilumab received marketing authorization (MA) in 2019, supported by the LIBERTY NP SINUS-24 and -52 studies; omalizumab obtained MA for uncontrolled CRS with polyposis in 2020, supported by the POLYP 1 and POLYP 2 studies; and mepolizumab has MA since January 2022, based on the SYNAPSE study. Clinical trials have also been conducted with reslizumab and benralizumab, but they are currently not approved for this indication. The three biologic agents indicated for the treatment of CRS with polyposis were evaluated for their efficacy and safety in adult patients:

- **Omalizumab:** anti-IgE monoclonal antibody approved in the European Union and United States for the treatment of severe allergic asthma[19]. Given the high levels of total IgE in nasal secretions, polyps, and serum of patients with CRS with polyposis, combined with its relevance in patients with allergic asthma, omalizumab has been evaluated as a potential treatment for the subgroup of patients with CRS with polyposis and comorbid asthma. In addition, eosinophilia

Figure 2
Indications for endoscopic sinus surgery



occurs in more than 80% of Caucasian patients with CRS with polyposis.

- **Mepolizumab:** human monoclonal antibody that prevents binding of circulating free IL-5 to the α subunit of IL-5R (IL-5Ra), which is expressed on the surface of eosinophils[20]. IL-5 is a key mediator in eosinophil chemotaxis, differentiation, activation, and survival, and demonstrates high levels in patients with CRS with polyposis.
- **Dupilumab**: human monoclonal antibody that binds to the α subunit of the IL-4 receptor (IL-4Rα), thus inhibiting the signaling of IL-4 and IL-13, two cytokines associated with type 2 T helper (Th2) cell activity that play an important role in the pathogenesis of nasal polyposis[21]. This therapy has already shown clinical benefits in patients with asthma and atopic eczema. Until 2019, monoclonal antibodies could only be prescribed to patients with concomitant severe asthma. In 2019, a group of researchers from the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA) developed criteria for the use of biologics in patients with CRS with polyposis, with or without concomitant asthma[22] (Fig. 3). In 2020, the board of the European Position Paper on Rhinosinusitis and Nasal Polyps 2020 made some modifications to these criteria[1] (Fig. 4). Biologics are currently approved as a complementary therapy to intranasal corticosteroids for the treatment of adults with CRS with nasal polyps, in whom systemic corticosteroids and surgery (unless contraindicated) have not provided adequate disease control.

In clinical terms, CRS with severe sinonasal polyposis is defined as a bilateral disease with at least 4 (out of 8) points on the Meltzer clinical scoring system of nasal polyposis (Endoscopic Nasal Polyps Score [NPS]) and persistent symptoms, including anosmia/ageusia, nasal obstruction, anterior and/or posterior rhinorrhea, and facial pain/pressure, requiring other therapeutic options to complement treatment with topical corticosteroids (systemic corticosteroids and/or surgery)[1]. When treatment fails, uncontrolled CRS is defined as a persistent or recurrent disease despite long-term treatment with topical corticosteroids and at least one course of systemic corticosteroids in the previous two years (or having a medical contraindication or intolerance to systemic corticosteroids) and/

Figure 3
Indications for biologics, European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA).

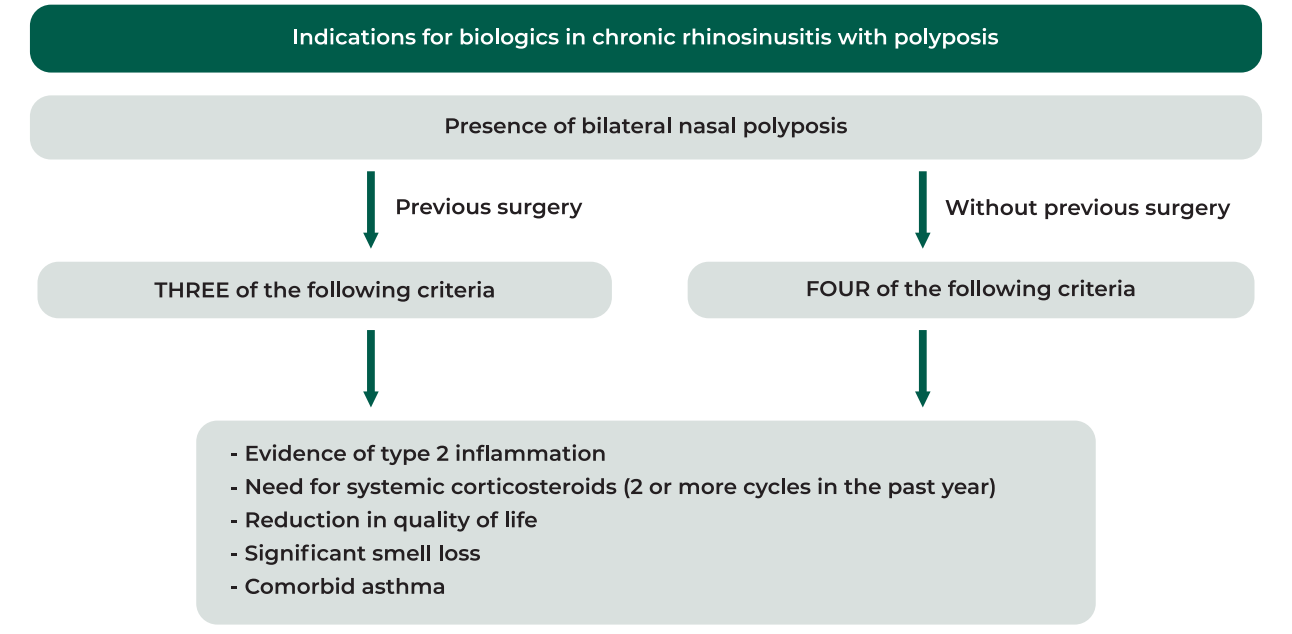
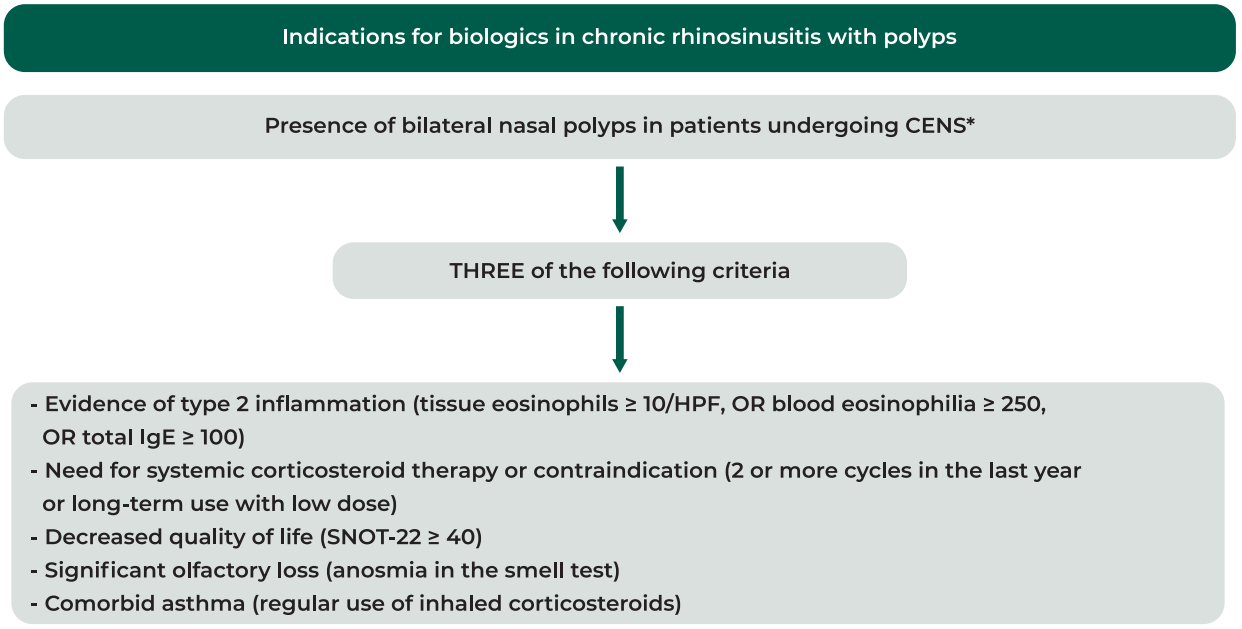
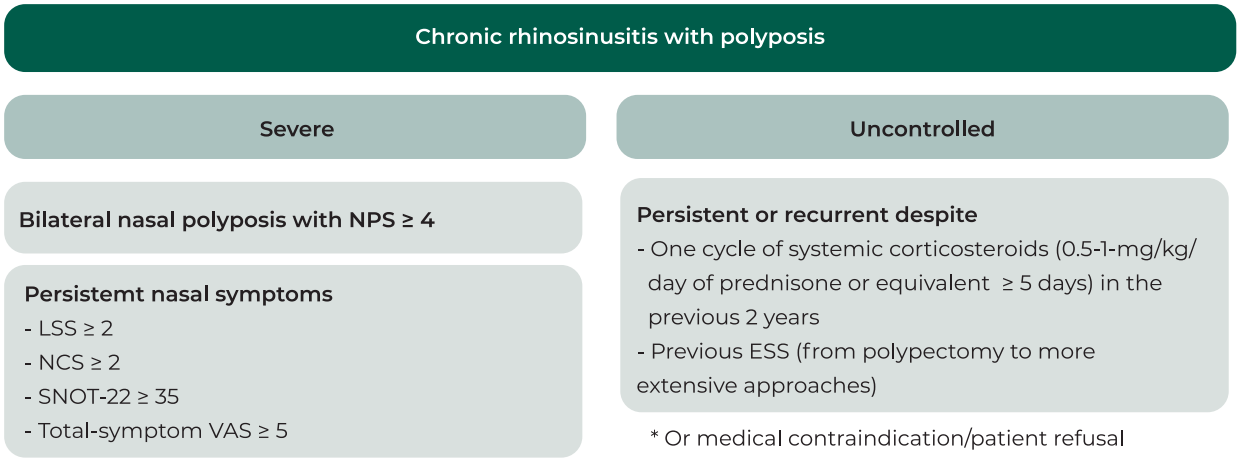


Figure 4
Indications for biologics, the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020.



*exceptional circumstances are excluded (e.g., without conditions for durgery). ESS, endoscopic sinonasal surgery

Figure 5
Chronic rhinosinusitis with severe and uncontrolled polyposis



* Or medical contraindication/patient refusal

or previous sinonasal surgery (unless there is a clinical contraindication for surgery)[1].

Biologic agents are indicated for patients with CRS with serious/severe sinonasal polyposis that is not controlled with conventional treatment (surgery and/or systemic corticosteroids always in association with the initial pharmacological treatment)[1]. It is important to establish a therapeutic algorithm for the management of CRS with polyposis that takes into consideration the initial pharmacological treatment, surgical treatment, and treatment with biologic agents in patients with severe disease that is difficult to control.

Methods

The proposals of the two main international working groups on this topic, the European Position Paper on Rhinosinusitis and Nasal

Polyps 2020 (EPOS) and European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA)[2] were reviewed, as were the methods used in several clinical trials of biologics in CRS with polyposis. The protocol proposal includes:

- Evaluation of demographic and clinical data.
- Scales of evaluation and forms of application.
- Criteria for treatment with dupilumab.
- Suggested evaluations during follow-up and criteria for efficacy and suspension of treatment.

Results

Clinical protocol

Demographic and clinical data

Demographic and clinical data included age, sex, assessment of the presence of asthma/atopy/hypersensitivity to non-steroidal anti-inflammatory drugs (NSAIDs), smoking status, number and type of previous sinonasal surgeries, number of cycles of systemic corticosteroids in the previous two years, nasal polyposis and rhinosinusitis severity assessment scales, Lund-Mackay score assessment, quantification of eosinophils in the peripheral blood, quantification of tissue eosinophils in patients who previously underwent ESS, and dosage of total IgE.

Evaluation scales

Endoscopic Nasal Polyps Score (NPS)

The endoscopic NPS is a score between 0 and 4 for each side, according to the size of the polyps, and is assessed by nasal endoscopy (Fig. 6). The maximum score is 8 points[23]. An NPS ≥5 (and ≥2 for each side) was used as an inclusion criterion in all clinical trials of biologics[24-27].

Loss of smell score (LSS)

Loss of smell is classified into four categories: 0 – without loss of smell/normosmia, 1 – mild hyposmia, 2 – moderate hyposmia, and 3 – severe loss of smell/anosmia[17]. In clinical trials and some specialized centers, this assessment is performed using computer software/records. As this approach is difficult to implement in clinical practice, we propose to apply this scale by enquiring about the average severity of smell loss in the last week, as was performed in the screening phase of one of the clinical trials[25] (Fig. 7). There are also psychophysical tests for smell assessment, such as the 40-item smell test[28] (The 40-item University of Pennsylvania Smell Identification Test - UPSIT) (Fig. 7). However, since they are not available in all centers, we think that they should be included only as complementary information.

Nasal Congestion Score (NCS)

Daily assessment of nasal congestion is classified into four categories[29]: 0 - without nasal congestion, 1 – mild nasal congestion, 2 - moderate nasal congestion, and 3 – severe nasal congestion. Similar to the LSS, the proposal is to apply this scale by enquiring about the average nasal congestion in the last week[25] (Table 1).

22-item Sinonasal Outcome Test (SNOT-22)

This instrument measures the CRS-specific quality of life in the previous 2 weeks and

Figure 6
Endoscopic nasal polyps score

Stadium
0 - Absence of polyps
1 - Small polyps in the middle meatus/edema
2 - Blockage of the middle meatus
3 - Polyps extend beyond the middle meatus without causing complete nasal obstruction
4 - Massive nasal polyposis

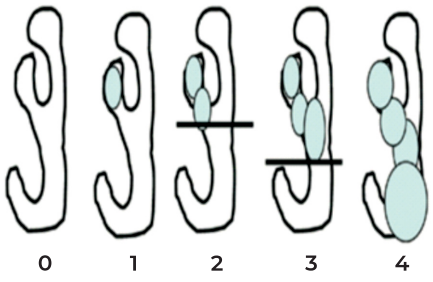
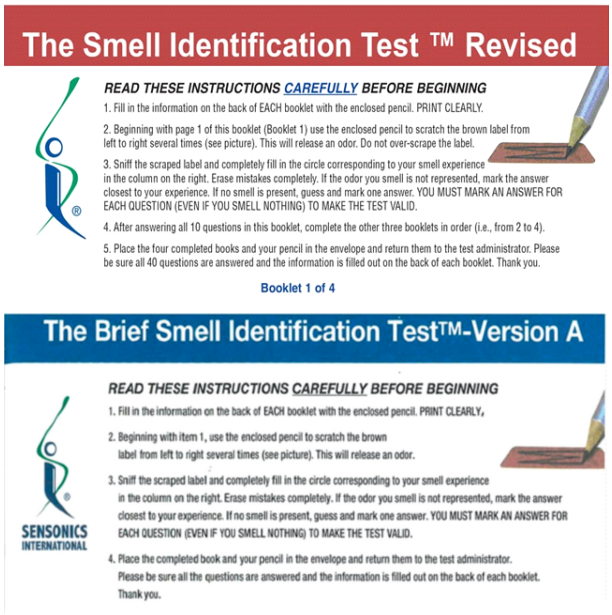


Figure 7
Loss of smell score (LSS) and The 40-item University of Pennsylvania Smell Identification Test (UPSIT).

Regarding the past week, how would you define the severity of nasal congestion (circle the corresponding number on the scale):

NCS - Nasal congestion (stuffy nose):

0 - No nasal congestion
1 - Mild nasal congestion
2 - Moderate nasal congestion
3 - Severe (very stuffy nose)


The Smell Identification Test ™ Revised

READ THESE INSTRUCTIONS CAREFULLY BEFORE BEGINNING

1. Fill in the information on the back of EACH booklet with the enclosed pencil. PRINT CLEARLY.
2. Beginning with page 1 of this booklet (Booklet 1) use the enclosed pencil to scratch the brown label from left to right several times (see picture). This will release an odor. Do not over-scrape the label.
3. Sniff the scraped label and completely fill in the circle corresponding to your smell experience in the column on the right. Erase mistakes completely. If the odor you smell is not represented, mark the answer closest to your experience. If no smell is present, guess and mark one answer. YOU MUST MARK AN ANSWER FOR EACH QUESTION (EVEN IF YOU SMELL NOTHING) TO MAKE THE TEST VALID.
4. After answering all 10 questions in this booklet, complete the other three booklets in order (i.e., from 2 to 4).
5. Place the four completed books and your pencil in the envelope and return them to the test administrator. Please be sure all 40 questions are answered and the information is filled out on the back of each booklet. Thank you.

Booklet 1 of 4

The Brief Smell Identification Test™-Version A

READ THESE INSTRUCTIONS CAREFULLY BEFORE BEGINNING

1. Fill in the information on the back of EACH booklet with the enclosed pencil. PRINT CLEARLY.
2. Beginning with item 1, use the enclosed pencil to scratch the brown label from left to right several times (see picture). This will release an odor.
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4. Place the completed book and your pencil in the envelope and return them to the test administrator. Please be sure all the questions are answered and the information is filled out on the back of each booklet. Thank you.

SENSONICS INTERNATIONAL

assesses the severity of symptoms and social and emotional problems related to the condition. The score ranges from 0 (no interference) to 110 (maximum interference with the quality of life), and the minimal clinically important difference (MCID) is 8.9 points[30]. The questionnaire that has been validated in Portuguese in Portugal[31] is shown in Table 2.

Total symptom Visual Analog Scale (VAS)

This scale assesses the patient's perception of the severity of all rhinosinusitis symptoms in the last month by drawing a vertical line in a 10-cm scale[32] (0 – minimum up to 10 – maximum (Table 3).

Table 1
Nasal congestion score (NCS)

With regard to the past week, how do you define the severity of (circle the corresponding number in the scale):

LSS – Loss of smell score

0 - Without loss of smell
1 - Mild loss of smell
2 - Moderate loss of smell
3 - Severe (no smell)

Criteria for inclusion for treatment with biologics

- Age ≥ 18 years.
- CRS with bilateral sinonasal polyposis in a patient who has previously undergone ESS or with a surgical contraindication and at least three of the following criteria:
  - Evidence of type 2 inflammation: tissue eosinophilia ≥ 10 eosinophils/high-power field or peripheral eosinophilia ≥ 250 or total IgE ≥ 100
    - Assess peripheral eosinophilia and/or total IgE if treatment with biologics is considered
    - In patients who underwent ESS and suspected type 2 inflammation, assess tissue eosinophilia (data on the disease endotype remains in case treatment with biologics is needed)
  - Need for systemic corticosteroids (≥ 2 courses/year or for more than 3 months) or systemic corticosteroids contraindicated
  - Significantly compromised quality of life (SNOT-22 score ≥ 40 points)
  - Anosmia in smell assessment (LSS)
  - Diagnosis of asthma (asthma requiring regular inhaled corticosteroids)

Table 2
22-item sinonasal outcome test (SNOT-22)

SNOT-22 – Below you will find a list of symptoms and social/emotional problems that affect patients with rhinosinusitis. Please answer the following questions about your symptoms. Give a score to your problems in the last two weeks.
Thank you for your participation. Ask for assistance if you have any problem filling the questionnaire.

Considering the severity of the problems, classify the intensity of the symptoms by circling the corresponding number in the scale:	No problem	Very mild problem	Mild problem	Moderate problem	Severe problem	Worst possible problem
1. Need to blow the nose	0	1	2	3	4	5
2. Sneezing	0	1	2	3	4	5
3. Runny nose	0	1	2	3	4	5
4. Cough	0	1	2	3	4	5
5. Discharge from the nose down into the throat	0	1	2	3	4	5
6. Thick discharge from the nose	0	1	2	3	4	5
7. Full or plugged-up ear sensation	0	1	2	3	4	5
8. Dizziness or vertigo	0	1	2	3	4	5
9. Ear pain	0	1	2	3	4	5
10. Facial pain or pressure	0	1	2	3	4	5
11. Difficulty going to sleep	0	1	2	3	4	5
12. Waking up during the night	0	1	2	3	4	5
13. Lack of a good night sleep	0	1	2	3	4	5
14. Waking up tired	0	1	2	3	4	5
15. Fatigue or tiredness during the day	0	1	2	3	4	5
16. Reduced productivity in everyday activities	0	1	2	3	4	5
17. Reduced capacity to perform everyday activities	0	1	2	3	4	5
18. Frustrated, agitated, irritated	0	1	2	3	4	5
19. Sadness	0	1	2	3	4	5
20. Feeling of shame	0	1	2	3	4	5
21. Difficulty in smelling and tasting	0	1	2	3	4	5
22. Blocked nose	0	1	2	3	4	5
Total score (sum):						

Table 3
Visual analog scale for all symptoms (VAS for total sinonasal symptom score)

Visual Analog Scale of Total Symptoms
Draw a vertical line at the point that best corresponds to how bothersome the symptoms of sinusitis have been in the last month.

Not bothersome at all	More than I can imagine

Proposal for monitoring the efficacy/safety and criteria for efficacy and suspension of treatment with biologics

ORL consultations after initiating treatment with Dupilumab

1ST CONSULTATION
4 weeks: evaluation of side effects

↓

2ND CONSULTATION
16 weeks: 1st evaluation of the response to treatment

↓

3RD CONSULTATION
24 weeks: 2nd evaluation of the response to treatment (maximum limit for response)

↓

4TH CONSULTATION
12 months: 3rd evaluation of the response to treatment for responders at 6 months

Evaluation of side effects: 1st consultation

- Evaluation at 4 weeks -

The most frequent adverse reactions during treatment with dupilumab (the only treatment with a funded therapeutic indication in Portugal at the moment) are: reactions at the injection site (erythema, edema, pruritus, and pain), conjunctivitis, allergic conjunctivitis, arthralgia, oral herpes, and eosinophilia. Rare cases of serum sickness reaction, serum sickness-like reaction, anaphylactic reaction, and ulcerative keratitis have been reported.

Reasons for immediate suspension:

- **Systemic hypersensitivity reaction (immediate or delayed):** anaphylactic reaction and angioedema occur within a few minutes or up to seven days after the dupilumab injection. The first dose should be monitored by an otorhinolaryngologist.
- **Helminthic infections:** if patients contract a helminthic infection while receiving treatment with dupilumab and do not respond to the antihelminthic treatment, dupilumab should be discontinued until the infection is resolved.

Evaluation of the response to treatment: 2nd consultation

- Evaluation of the response at 16 weeks -

Improvement required in at least one of the following criteria:

- **Reduction in the size of the polyps**
  - In at least 1 degree in nasal endoscopy (one nasal cavity) or 2 points (right nasal cavity + left): NPS - Endoscopic Nasal Polyps Score
- **Reduction in the need for systemic corticosteroids**
  - No need for systemic corticosteroids since the start of the treatment
- **Improvement in the quality of life**
  - Reduction ≥ 9 points in the SNOT-22
- **Improved smell**
  - Disappearance of anosmia
- **Reduction in nasal obstruction**
  - Improvement in the symptoms in the VAS: reduction ≥ 2 points

Evaluation of the response to treatment: 3rd consultation

- Evaluation of the response at 24 weeks -

Improvement required in at least one of the following criteria:

- **Reduction in the size of the polyps**
  - In at least 1 degree in nasal endoscopy (one nasal cavity) or 2 points (right nasal cavity + left): NPS - Endoscopic Nasal Polyps Score
- **Reduction in the need for systemic corticosteroids**
  - No need for systemic corticosteroids since the start of the treatment
- **Improvement in the quality of life**
  - Reduction ≥ 9 points in the SNOT-22
- **Improved smell**
  - Disappearance of anosmia

- Reduction in nasal obstruction
  - Improvement in the symptoms in the VAS: reduction ≥ 2 points

Evaluation of the response to treatment: 4th consultation

- Evaluation of the response at 12 months -

At this stage of treatment, it is necessary that all the following criteria are met:

- **Reduction in the size of the polyps**
  - NPS < 4 (in total, considering both nasal cavities) in nasal endoscopy
- **Improvement in the quality of life**
  - Total SNOT-22 score < 30
- **No need for systemic corticosteroids or ESS**
- **Reduction in nasal obstruction**
  - VAS score < 5

Discussion

CRS with nasal polyposis is a chronic inflammatory condition with a predominantly type 2 inflammation profile[1]. It continues to be an extremely important topic in otorhinolaryngology because of its high prevalence and impact on the patients' quality of life[1]. Its treatment can be divided into medical and/or surgical. Biologic agents have emerged as an important therapeutic weapon for the control of this disease and comorbidities with a type 2 inflammatory component[22].

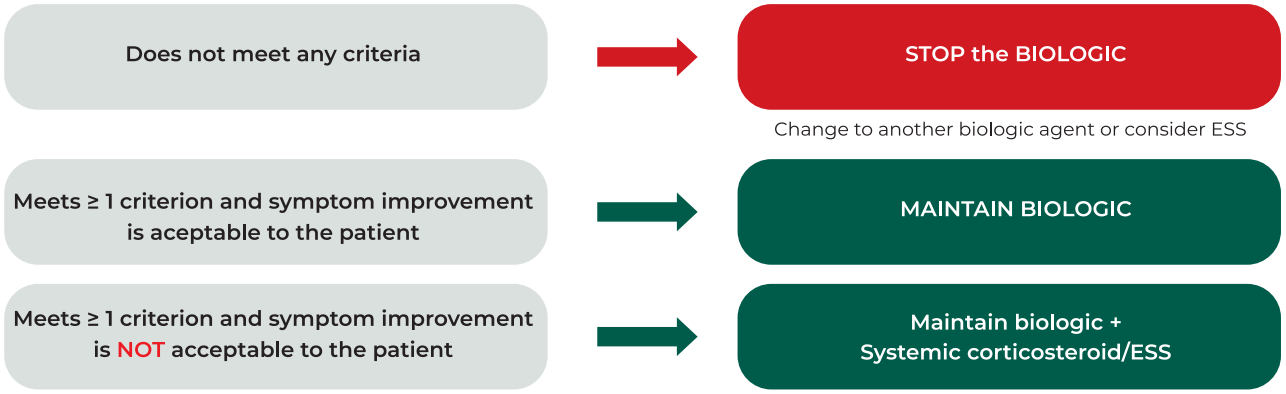
Based on these assumptions, a working group was set up at Hospital Pedro Hispano that included otorhinolaryngology specialists and interns, with the aim of proposing criteria for the prescription of biologic agents in patients with CRS with polyposis, as well as measures for assessment of cross-sectional efficacy

Table 4
List of adverse reactions

MedDRA Class of organ systems	Frequency	Adverse reaction
Infections and infestations	Frequent	Conjunctivitis* Oral herpes*
Blood and lymphatic system diseases	Frequent	Eosinophilia
Immune system diseases	Not very frequent Raros	Angioedema* Anaphylactic reaction Serum sickness reaction Serum sickness-type reaction
Ocular problems	Frequent Not very frequent Rare	Allergic conjunctivitis* Keratitis** Blepharitis* Eye itching* Dry eye* Ulcerative keratitis*
Problems of skin and subcutaneous tissues	Not very frequent	Facial skin eruption*
Problems of musculoskeletal and connective tissues	Frequent	Arthralgia*
General problems and changes in the site of administration	Frequent	Reactions at the site of injection (including erithema, edema, itching, pain, and swelling)

Very frequent (≥ 1/10); frequent (≥ 1/100, < 1/10); not very frequent (≥ 1/1000, < 1/100); rare (≥ 1/10 000, < 1/1000); very rare (< 1/10 000).
Within each group of frequency, the adverse reactions are presented in decreasing order of severity.

Figure 8
Evaluation of the response at 16 weeks. ESS, endoscopic sinus surgery



(regardless of the administered biologic agent) and standardized data collection that allows uniform assessment and multicenter prospective and/or retrospective studies. Nationally and internationally validated scales were applied for data collection and eligibility assessment[23-32].

Endoscopic evaluation of nasal polyps is one of the fundamental steps of the protocol, and treatment with biologic agents is indicated in patients with serious/severe polyposis (Endoscopic NPS ≥ 4). In our protocol, we opted for the NPS because this scale was used for the development of criteria for treatment with biologics in patients with CRS with polyposis by EUFOREA[22]. The main limitation of this scale is that it does not assess polyps arising in the ethmoidal notch, which does not allow comparisons with the results of trials using a different scale (e.g., the Lildholdt scale). To standardize the assessment and quantification of nasal polyposis in clinical

Figure 9
Evaluation of the tratmnet response at 24 weeks. ESS, endoscopic sinus surgery

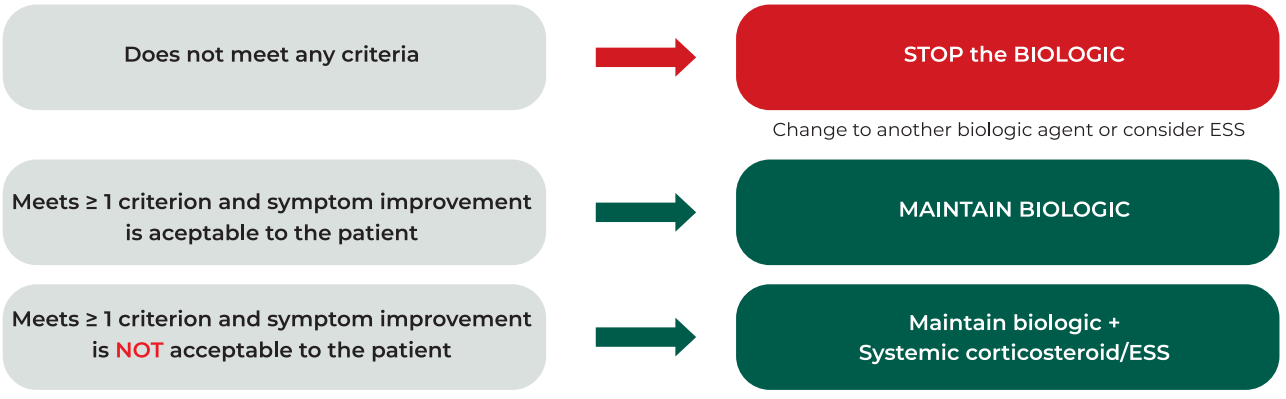
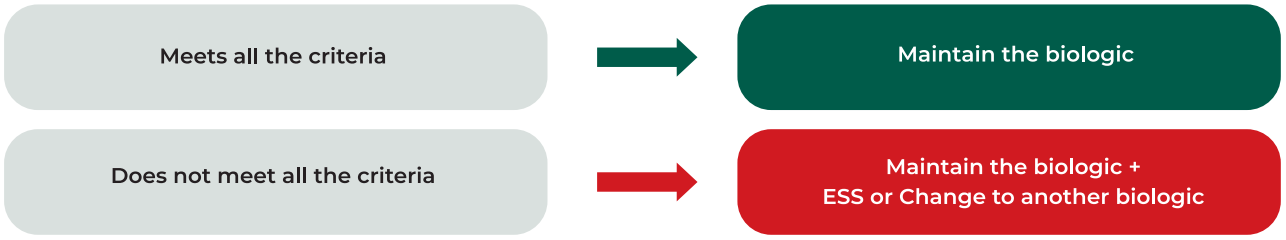


Figure 10
Evaluation of the response to treatment at 12 months.



trials, a recent paper[33] suggested summing the grades of different scales, which could help in overcoming the anatomic limitations of each one. A point not mentioned in the clinical protocol is related to the referral of comorbidities.

Because CRS with polyposis is often accompanied by conditions with a type 2 inflammatory component, such as allergic asthma and hives, these patients clearly benefit from a multidisciplinary group consultation (e.g., otorhinolaryngology, pulmonology, and allergy and immunology). This aspect is particularly relevant in patients with CRS with polyposis and comorbid allergic asthma; for example, patients with CRS with polyposis without comorbid asthma who do not respond to dupilumab do not have a funded therapeutic indication (at the moment) for omalizumab. However, if they also have severe persistent asthma, they are eligible for it.

The clinical protocol presented herein provides a standardized method for data collection and proposes inclusion criteria based on international consensuses[1,22] for the treatment of patients with CRS with polyposis with biologic agents. It also provides guidelines for the follow-up of these patients, with well-defined criteria for continuation and discontinuation of treatment.

Conclusion

This clinical protocol presents a proposal for the standardized and uniform collection of data for use in clinical practice and multicenter prospective and/or retrospective studies, as well as a proposal for patient follow-up and evaluation of the efficacy/failure of treatment with biologic agents in patients with CRS with polyposis.

Conflict of interest

The authors declare no conflict of interest regarding this article.

Data confidentiality

The authors declare that they followed the protocols in use at their working center regarding the publication of patients' data.

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Availability of scientific data

There are no publicly available datasets related to this study.

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