Spanish Consensus on the Management of Chronic Rhinosinusitis With Nasal Polyps (POLIposis NAsal/POLINA 2.0)

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) is a highly prevalent and burdensome disease for both individuals and health systems. Its management involves many specialties, including otorhinolaryngology, allergology, pulmonology, primary care, pharmacy, and pediatrics. A multidisciplinary approach and the participation of the patient in decision-making are essential, both for diagnosis and for therapy. The authors of the consensus aim to translate current knowledge into an easy-to-read practical guide and emphasize those aspects requiring further discussion or with unmet needs owing to the lack of appropriate scientific evidence. An iterative approach for the development of an evidence-based systematic review with recommendations was followed using a standard quality assessment approach (Scottish Intercollegiate Guidelines Network [SIGN] and National Institute for Health and Care Excellence [NICE]). The guideline was critically evaluated using the Appraisal of Guidelines for Research and Evaluation (AGREE II) and Recommendation Excellence (AGREE REX) instruments. Consequently, POLINA has been considered a high-quality guideline by an independent agency.
The POLINA consensus provides new definitions of control, therapeutic management (including surgery and evaluation of severity), indications for use of biologics, and response. Finally, this guideline focuses on unmet research needs in CRSwNP.

Key words: Asthma. Biologics. Chronic rhinosinusitis. Corticosteroids. CRSwNP. Endoscopic sinus surgery. Guideline. Nasal polyps. N-ERD. Type 2 inflammation.

Resumen

La rinosinusitis crónica con pólipos nasales (RSCcPN) es una enfermedad de alta prevalencia y onerosa para las personas y los sistemas de salud cuyo manejo involucra a muchas especialidades: otorrinolaringología, alergología, neumología, atención primaria, farmacia y pediatría. El abordaje multidisciplinar y la participación del paciente en la toma de decisiones son fundamentales, tanto para el diagnóstico como para la estrategia terapéutica. Los autores del consenso pretenden traducir los conocimientos actuales en una guía práctica de fácil lectura y enfatizar aquellos aspectos en los que todavía hay discusión o necesidades no cubiertas por falta de evidencia científica adecuada. Se utilizó un enfoque iterativo para el desarrollo de una revisión sistemática basada en evidencia con recomendaciones, utilizando un esquema de evaluación de calidad estándar (*Scottish Intercollegiate Guidelines Network* -SIGN- y *National Institute for Health and Care Excellence* -NICE-), y una evaluación crítica de la directriz se ha llevado a cabo a través del instrumento Evaluación de Directrices para la Investigación y Evaluación (AGREE II) y Recomendación de Excelencia (AGREE REX). Con base en lo anterior, la guía POLINA ha sido considerada una guía de buena calidad por una agencia independiente.

El consenso POLINA aporta nuevos esquemas para la definición de control, manejo terapéutico incluyendo evaluación de gravedad, indicaciones de la cirugía y del uso de biológicos, y la respuesta al tratamiento. Finalmente, esta guía se enfoca en las necesidades de investigación insatisfechas en la RSCcPN.

Palabras clave: Asma. Biológicos. Rinosinusitis crónica. Corticosteroides. Rinosinusitis nasal con poliposis nasal. Cirugía endoscópica de senos. Guías. Poliposis nasal. EREA. Inflamación tipo 2.

Introduction

Chronic rhinosinusitis (CRS) is an inflammatory disease of multifactorial etiology involving the immune system and epithelial barrier responses. It is influenced by the microbiome, the environment, and genetic and epigenetic factors [1,2]. CRS affects 11%-13% of the general population [3,4] and has a negative impact on quality of life (QOL) [5,6]. It also affects sleep quality and increases somnolence and the risk of sleep apnea [7]. The 2 main phenotypes of CRS are with nasal polyps (CRSwNP) and without nasal polyps (CRSsNP), the former accounting for 18%-20% of all CRS cases [8]. In Europe, the annual cost of CRSwNP is about €7160 per patient annually, with direct costs reaching €1501, mainly derived from medical consultations and hospitalization, and indirect costs reaching €5659, resulting from loss of work productivity [9].

CRSwNP is predominantly associated (85%) with type 2 (T2) inflammation in western countries and is caused by the production of T2 cytokines such as alarmins, IL-4, IL-5, and IL-13, which results in tissue eosinophilia [10-12].

One-quarter of patients with CRS have asthma, while 20% of asthma patients have CRS [13]. The asthma that accompanies CRSwNP is usually late-onset and nonatopic and is associated with greater severity, poorer control, more frequent exacerbations, and lower QOL than CRSsNP [14,15]. In severe asthma, up to 43% of patients present CRSwNP, with a longer duration of nasal symptoms and an increased number of sinus surgeries [13,16]. The comorbidity NSAID-exacerbated respiratory disease (N-ERD) affects up to 26% of CRSwNP patients [15,16], in whom sinonasal disease is more severe, the risk of postsurgical recurrence is high, and the disease coexists with more severe and uncontrolled asthma [17,19].

A variety of specialties participate in the management of CRSwNP, including otorhinolaryngology, pulmonology, allergology, primary care, pharmacy, and pediatrics. Consequently, a multidisciplinary approach is considered essential for both diagnostic and therapeutic strategies [20]. CRSwNP is clinically diagnosed by the presence of sinonasal symptoms such as nasal obstruction or congestion, rhinorrhea (anterior and/or posterior), smell dysfunction, and/or facial pressure and pain. Therefore, diagnosis of CRS requires the presence of 2 or more cardinal symptoms, 1 of which must always be nasal congestion or rhinorrhea lasting for more than 12 weeks without resolution, together with diagnostic signs on nasal endoscopy (mucus secretion or nasal polyps in the middle meatus) or on a sinonasal CT scan (opacification of paranasal sinuses) (Table 1) [1].

The treatment of CRSwNP is based on 3 approaches: (*1*) appropriate/optimal medical treatment, (*2*) surgical treatment when there is no optimal response to medical treatment, and (*3*) biological therapy in severe uncontrolled disease. Since there is a growing consensus that the goal of treatment is to maintain clinical control of CRSwNP, identifying patients with poorly controlled disease after a regular assessment is necessary to guide the therapeutic response [1]. However, current instruments for disease control are inconsistent regarding the criteria used to define control and the items included [21].

POLINA.1 (POLIposis NAsal), the Spanish guideline on management of CRSwNP, was published a decade ago [22]. The main objective of the present document (POLINA.2) is to collect the best scientific evidence for each aspect of the disease (epidemiology, pathophysiology, disease burden, diagnosis, treatment, and short/long term follow-up) since then. The authors aimed to translate current knowledge into an easy-to-read practical guide and emphasize those aspects in which there is still discussion or unmet needs owing to the lack of proper scientific evidence. New algorithms for treatment of mild-to-moderate CRSwNP in the era of biologics are also included. In addition, disease control and criteria for the indication of and response to biologic agents are widely discussed. Finally, this guideline focuses on research into unmet needs in CRSwNP.

Table 1. POLINA Recommendations on Diagnosis of Chronic Rhinosinusitis With Nasal Polyps.

Diagnosis is based on sinonasal symptoms and the presence of bilateral nasal polyps in nasal endoscopy.	A
Nasal symptoms should be assessed subjectively using a Likert or visual analog scale.	B
When establishing the endotype, blood eosinophil count and total IgE show the association with type 2 inflammation. Skin tests and/or determination of serum specific IgE serve to confirm patient sensitivities to common allergens.	B
It is recommended to carry out pheno-endotyping for the histopathological study of nasal polyps (biopsy) and rule out other diseases (benign or malignant).	B
The sense of smell should be assessed using validated olfactometry.	B
Since it is very complex to predict the improvement in smell after surgery, it is currently not recommended to use this isolated symptom as an indication for surgery.	B

Literature Search and Methodology

We applied an iterative approach for the development of an evidence-based systematic review with recommendations using a standard quality assessment approach (Scottish Intercollegiate Guidelines Network [SIGN] and National Institute for Health and Care Excellence [NICE]) (Supplementary Table 1-2S) [23,24].

The guideline was externally reviewed by specialists in methodology from the Institute for Health and Clinical Excellence (INPECS) with a double objective: first, to assess the scientific quality of the POLINA guideline and its recommendations; and second, to analyze its structure, content, and presentation. This critical evaluation of the POLINA guideline was carried out using the instrument Appraisal of Guidelines for Research and Evaluation (AGREE II) [25], which evaluates both the methodological rigor and transparency of the guideline during the drafting process and the credibility of the recommendations, as well as the possibility of their implementation through the AGREE Recommendation Excellence (AGREE REX) instrument [26]. Three external reviewers read the POLINA guideline independently using both instruments, which were completed by responding to various items (23 in the case of AGREE II and 9 in the case of AGREE REX) according to the degree of agreement. The items were grouped into a series of domains (6 in AGREE II, namely, scope and objective, participation of those involved, rigor in the elaboration, clarity of presentation, applicability, and editorial independence; and 3 in AGREE REX, namely, clinical applicability, values and references, and implementation), for which an overall score was expressed as a percentage of the weighted score of the reviewers who evaluated the document. A higher percentage expressed higher quality of the domain evaluated. Based on the foregoing, POLINA was considered a high-quality guideline by the Institute for Clinical and Health Excellence (Supplementary Tables 3 and 4).

Type 2 Inflammation

In response to tissue damage, cells of the sinonasal epithelium produce alarmins such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. TSLP is essential for initiating the T2 immune response through activation of ILC2 and T_H2 lymphocytes [27,28]. Once activated, ILC2, T_H2 cells, eosinophils, and mast cells are important sources of T2 cytokines (IL-4, IL-5, and IL-13), which participate in both the innate and the adaptive immune response. Immunity is stimulated through the humoral cytokines IL-4 and IL-13 by activating B lymphocytes, which produce polyclonal IgE [29,30].

In CRSwNP, *Staphylococcus aureus* produces enterotoxins that act as superantigens, giving rise to an increased response by lymphocytes, which interact with a large proportion of T or B cells through their antigen receptor, and producing a polyclonal IgE response [31]. Eosinophils play a very important role in CRSwNP, since their recruitment, activation, and survival are regulated by epithelial cytokines, eicosanoids, and exogenous proteases, in addition to IL-5 [32]. Eosinophils are abundant in the tissues of the patients with CRSwNP and type 2 inflammation and are considered a biomarker of severe disease and of an indolent clinical course [33,34].

Disease Control

An increasing number of studies are exploring disease control in patients with CRSwNP. It is important to note that the parameters for evaluating disease control in CRSwNP differ across studies [21]. The primary goal of any therapy, especially in chronic conditions, is to achieve and maintain clinical control, which can be defined as a disease state in which the patient does not experience symptoms or the symptoms do not impact QOL [1]. Whereas asthma control assessment criteria have been recommended as good clinical practice [35] and poor asthma control has been correlated with high sinus CT scores in CRSwNP [36], control of CRSwNP is not routinely assessed in daily clinical practice, and a clear consensus on assessment criteria has not yet been reached.

The European Position Paper on Rhinosinusitis (EPOS) 2020 proposed a clinical staging system for disease control in CRSwNP [1]. *Control* is defined as a disease state free from bothersome symptoms and having a healthy mucosa. According to the EUFOREA group, *uncontrolled* CRSwNP is defined as "persistent or recurring despite long-term treatment with intranasal corticosteroid (INCS) and having received at least 1 course of systemic corticosteroids in the preceding 2 years … and/or previous sinonasal surgery" [37]. However, this initial proposal has been acknowledged to be opinion-based and not data-driven, and validation studies have shown that assessment of disease control using EPOS has slight agreement with patients and a physician [38]. Given the

Table 2. POLINA Criteria for the Control of Chronic Rhinosinusitis With Nasal Polyps.

	Controlled (all of the following)	Partially controlled (at least 1 present)	Uncontrolled (3 or more present)
Severity of disease VAS (0-10 cm)	0-3	>3-7	>7-10
Loss of smell VAS (0-10 cm)	0-3	>3-7	>7-10
Quality of life (SNOT-22) (0-110)	8-20	>20-50	>50
Endoscopic nasal polyp score (0-8)	Maximum of 1 in each nasal cavity	Total score <5	Total score ≥5
Use of SCS in the previous year (Short courses)	No	1-2[a]	>2[a]
Need for surgery[b]	No	No	Yes

Abbreviations: SCS, systemic corticosteroids; SNOT-22, Sino-Nasal Outcome Test 22; VAS, visual analog scale.
[a]Short course from 5 d at a dose of 0.5-1 mg/kg/d.
[b]Endoscopic sinus surgery with opening of the affected sinuses.

importance of the concept of disease control, from a clinical and from a research perspective, there remains a need for a gold standard to assess disease control in CRSwNP.

The POLINA expert committee proposes using the following assessments to define control of CRSwNP: disease severity and loss of smell (visual analog scale [VAS], 0-10 cm), impairment of QOL (Sino-Nasal Outcome Test [SNOT-22], 0-110), nasal endoscopic examination (nasal polyp score [NPS], 0-8), use of systemic corticosteroids in the previous year, and the need for surgery. Control of CRSwNP is classified into 3 categories: controlled, partially controlled, and uncontrolled (Table 2). Disease control status should be assessed periodically in order to guide the stepwise approach to optimizing CRSwNP management.

The results of the EPOS 2020 studies and the recommendations for future research described in POLINA, together with the arrival of mHealth technologies, will hopefully facilitate this process of validation in the coming years.

Patient Participation in Decision Making and Multidisciplinary Approach

For individual cases, shared decision-making is one of the 4 cardinal principles of precision medicine at the time of diagnosis and prediction of success of the treatment initiated, enabling the patient to participate in decisions regarding his/her treatment [1,39]. Moreover, patient involvement is recognized as a key component in the development of clinical practice guidelines, with important implications for guideline implementation. It necessarily brings together clinicians from many specialties, scientists, and, above all, patients in a collaborative effort to ensure the most efficient and effective management. Patient participation in the POLINA guideline is covered by representatives from the Asociación Española de Pacientes con Poliposis Nasal (AEPONA [Spanish Association of Nasal Polyposis Patients]), who were actively involved in the development of the guideline.

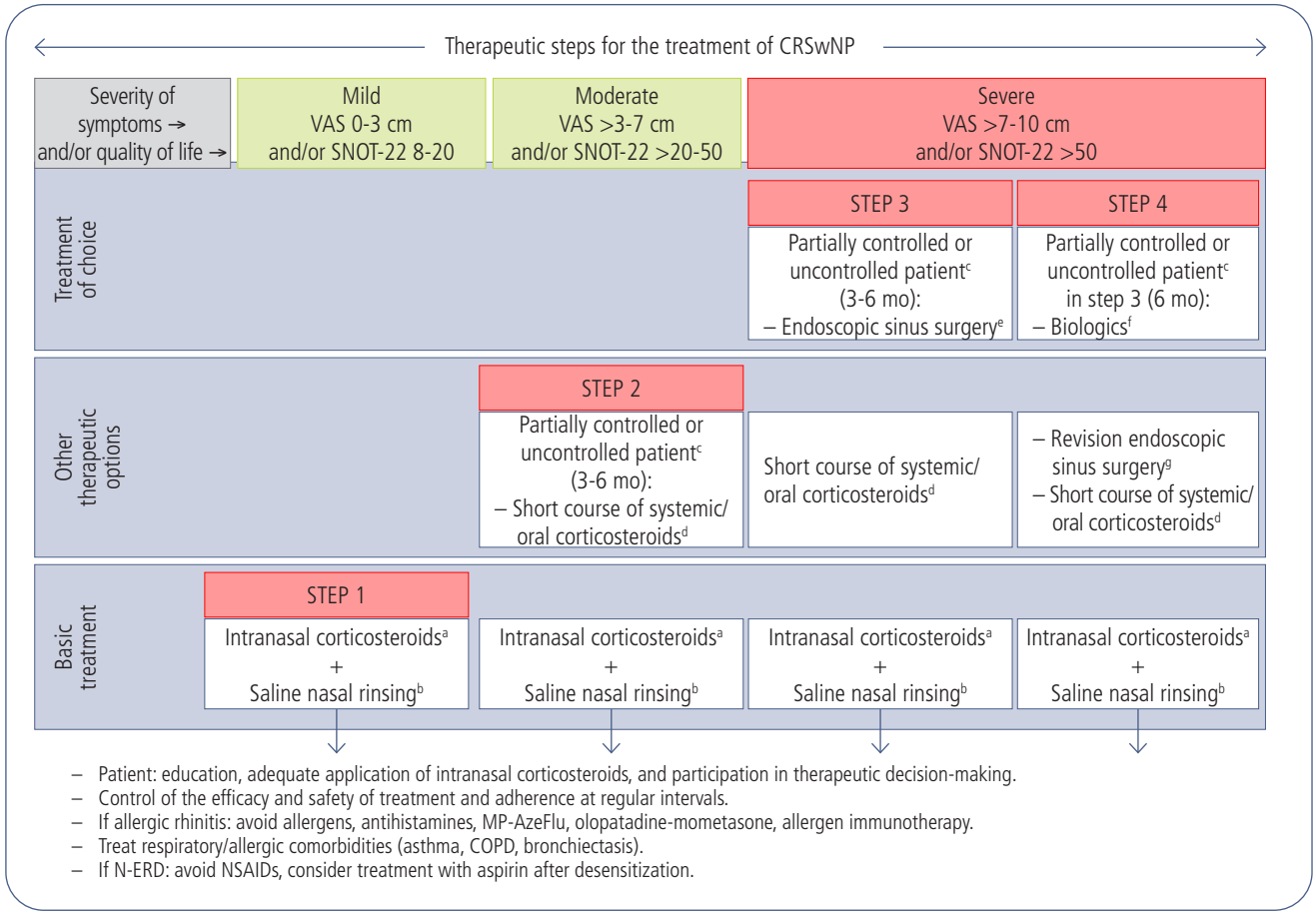

Figure 1. Therapeutic steps for the treatment of chronic rhinosinusitis with nasal polyps (CRSwNP). COPD indicates chronic obstructive pulmonary disease; NSAIDs, nonsteroidal anti-inflammatory drugs; N-ERD, NSAID-exacerbated respiratory disease; VAS, visual analog scale; SNOT-22, Sino-Nasal Outcome Test 22.
[a]Spray, drops, or rinsing.
[b]Rinsing with isotonic saline or lactated Ringer solution.
[c]See POLINA criteria for the control of CRSwNP (Table 2).
[d]Short courses from 5 days at a dose of 0.5-1 mg/kg/d.
[e]Opening of affected paranasal sinuses.
[f]Possible choice according to endotype.
[g]Evaluate more radical/extended surgery according to consensus between surgeon and patient.

Few qualitative studies on the patient's experiences and perspectives of current management of CRSwNP have been published. Those that have identify the patient's frustrations with delayed referral, lack of management of comorbidities, poor communication, inconsistency of advice, incorrect medication use, adherence to INCS, and lack of recognition of the impact of CRS [40,41].

A more holistic and multidisciplinary approach can be promoted through collaboration by a multidisciplinary team, in particular the improvement of communication between health professionals, the inclusion of CRSwNP in asthma/pulmonology/allergology guidelines, and the introduction of a "United Airway Disease" committee in hospitals [20,39]. Since patients now demand more independence in disease management, this empowerment can be achieved by implementing mobile health apps, organizing patient training on the correct use of medications, and customizing legislation regarding prescriptions for chronically ill patients [42,43].

Treatment of CRSwNP (Figure 1)

Appropriate Medical Treatment

Long-term INCS therapy is recommended as the first line in CRSwNP owing to its efficacy and safety, since it improves clinical parameters, reduces nasal polyp size, and prevents recurrences after surgery [1,19,44]. No differences have been demonstrated between INCS or administration devices [45-47]. Besides, poor adherence to INCS has been reported in patients with CRSwNP [48].

Short courses of systemic corticosteroids (SCS) can be used to treat CRSwNP exacerbations, although the effect is transitory. Since SCS can have significant adverse effects, it is recommended to balance their short-term benefit with their impact on bone metabolism (bone mass modification) [49].

Nasal rinsing with isotonic and hypertonic saline is effective in CRSwNP, improving both symptoms and QOL, while the use of large volumes is recommended over nasal saline spraying. The addition of xylitol or sodium hyaluronate to irrigation with nasal saline may have an additional positive effect [1,50,51].

Treatment with antihistamines is only recommended as an option in patients with CRSwNP associated with allergic rhinitis [52]. The use of short-term antibiotics (oral or intranasal) is not recommended in CRSwNP patients, and evidence for the long-term efficacy and safety of low-dose macrolides is still lacking. Low-dose macrolides could be useful in selected CRS patients [1], mainly those with CRSsNP. Antileukotrienes are not recommended in CRSwNP patients [53,54]. Available data indicate that the use of mucoactive agents, probiotics, phototherapy, proton pump inhibitors, verapamil, furosemide, and herbal medicines should be avoided in CRSwNP [1]. Table 3 summaries the POLINA recommendations.

Surgical Treatment

Surgery is an option after appropriate medical therapy has failed, although the appropriate extent of surgery is controversial [55]. The main goals of endoscopic sinus surgery (ESS) are to relieve sinonasal symptoms, to debride inflamed tissue, and to provide optimal delivery of topical intranasal therapy to the paranasal sinuses [56].

Table 3. POLINA Recommendations on Medical Treatment of Chronic Rhinosinusitis With Nasal Polyps.

Nasal saline rinsing and INCS are recommended as the first line of treatment.	A
No differences have been demonstrated between INCS or with higher doses or according to the administration device.	A
The use of INCS after surgery is recommended to prevent recurrences.	A
Short-course systemic corticosteroids can be used, although their effect is transitory, and safety is low.	A
Short- and long-term courses of antibiotics are not recommended.	B
Antileukotrienes are not recommended.	B
Despite the efficacy of aspirin desensitization in N-ERD patients, their use in clinical practice is not common owing to the high risk-benefit ratio.	B
Aspirin treatment after desensitization is not recommended for N-ERD patients.	B
The use of mucoactive agents, probiotics, phototherapy, proton pump inhibitors, verapamil, furosemide, and medicinal herbs is not recommended.	B

Abbreviation: INCS, inhaled corticosteroids; N-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.

ESS can be categorized as limited (simple excision of nasal polyps or polypectomy), functional, or radical. Regarding the extent of ESS, some studies advocate "full house" surgery, which includes complete sphenoidotomy and Draf IIA frontal sinusotomy rather than excising only the affected sinuses. This statement is based on the reduced need for revision surgery and greater improvement in nasal symptoms reported in patients undergoing more extensive surgery [57-58]. Table 4 provides the POLINA recommendations on surgical treatment.

Biological Therapy

Biologics constitute a therapeutic choice for patients with type 2 severe CRSwNP when classical treatment approaches do not provide symptom or disease control. Biologics are drugs produced from living organisms that target specific

Table 4. POLINA Recommendations on Surgical Treatment of Chronic Rhinosinusitis With Nasal Polyps.

Endoscopic sinus surgery should be considered the preferred option when adequate medical treatment is no longer effective, especially as the first intervention.	B
In the case of a first intervention, functional surgery is recommended.	D
Reboot surgery ± Draf III is recommended in patients with a high risk of recurrence (with multimorbid asthma and/or N-ERD).	C

Abbreviation: N-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.

Table 5. Efficacy and Safety of Biologics in Treatment of Severe Chronic Rhinosinusitis With Nasal Polyps.

Study	CRSwNP	Treatment	Variables	Results
Anti-IgE				
Gevaert et al, 2020 [61] RCT	POLYP 1: N=138 POLYP 2: N=127	Omalizumab every 2 or 4 wk for 24 wk SC, dose depends on blood IgE levels and weight (N=134) Placebo (N=131)	– NPS – Nasal congestion – SNOT-22 – UPSIT – Nasal symptoms – AQLQ – ESS – Adverse events	– Improvement in NPS and nasal congestion – Improvement in SNOT-22, UPSIT, hyposmia, and rhinorrhea – Improvement AQLQ – Reduction in ESS – Equal adverse events
Gevaert et al, 2013 [65] RCT	N=24	Omalizumab every 2 or 4 wk for 16 wk SC, dose depends on blood IgE levels and weight (N=16) Placebo (N=8)	– RSOM-31, AQLQ, SF-36 – Symptoms – NPS – LMS (CT) – Spirometry – Blood and nasal biomarkers – Adverse events	– Improvement in AQLQ, SF-36 (physical summary), some domains RSOM-31 – Improvement: nasal congestion, anterior rhinorrhea, hyposmia, and wheezing/dyspnea – Reduction in NPS and LMS – Reduction in total IgE and ECP only in nose – More common cold, 1 case of lymphoblastic lymphoma
Tiotiu et al, 2020 [82] Real life	N=24	Omalizumab every 2 or 4 wk for 24 wk SC, dose depends on blood IgE levels and weight 6 mo	– NPS – Sinonasal symptoms – LMS (CT)	– No improvement in NPS – Improvement in sinonasal symptoms – Improvement LMS (CT)
Anti–IL-5/5Rα e - IL-5				
Han et al, 2021 [62] RCT	SYNAPSE: N=407 Severe CRSwNP (1 or more previous ESS)	Mepolizumab 100 mg SC every 4 wk for 52 wk (N=206) Placebo (N=201)	– NPS – Nasal congestion (VAS) – Loss of smell (VAS) – Sinonasal symptoms – VAS-CRS – SNOT-22 – ESS – ACQ-5 – OCS use – Biomarkers: Blood eosinophils	– Improvement in NPS – Improvement in sinonasal symptoms, nasal congestion, loss of smell – Improvement in SNOT-22 – Improvement in VAS-CRS – Reduction in ESS – Improvement in ACQ-5 – Reduction in OCS use – Reduction in blood eosinophils
Bachert et al, 2017 [68] RCT	N=105	Mepolizumab 750 mg IV every 4 wk for 6 wk (N=54) Placebo (N=53)	– Indication for ESS – VAS-CRS – NPS – Sinonasal symptoms – UPSIT – SNOT-22, EQ-5D – PNIF – Eosinophils – FEV_1/FVC	– Reduction in ESS – Improvement in sinonasal symptoms (loss of smell), NPS, SNOT-22, PNIF, and VAS-CRS – Reduction in eosinophils – No significant differences in UPSIT, EQ-5Q, or lung function
Gevaert et al, 2011 [67] RCT	N=30 severe or recurrent CRSwNP	Mepolizumab 750 mg IV every 4 wk 2 doses (N=20) Placebo (N=10)	– NPS – CT (worse, better, without changes) – PNIF – Sinonasal symptoms – Biomarkers: eosinophils, ECP, IL-5Rα, IL5, IgE	– No change in sinonasal symptoms – Improvement in NPS and PNIF – No reduction: ECP, IL-5 Rα, IgE
Detoraki et al, 2021 [69] Real life	N=44	Mepolizumab (100 mg every 4 wk) 1 y	– NPS – SNOT-22	– Improvement in NPS – Improvement in SNOT-22

(continued)

Table 5. Efficacy and Safety of Biologics in Treatment of Severe Chronic Rhinosinusitis With Nasal Polyps (*continuation*).

Study	CRSwNP	Treatment	Variables	Results
Anti–IL-5/5Rα e - IL-5				
Gevaert et al, 2006 [66] RCT	N=24	Reslizumab 3 mg/kg IV 1 dose (N=8) Reslizumab 1 mg/kg IV 1 dose (N=8) Placebo (n=8)	– NPS – Sinonasal symptoms – PNIF – Eosinophils, ECP, eotaxin, IL-5	– No improvement in NPS, PNIF, sinonasal symptoms – Reduction in NPS only for 1 mg/kg – Reduction in eosinophils, ECP, and IL-5
Bachert et al, 2022 [63] RCT	OSTRO: N=413	Benralizumab 30 mg every 4 wk for first 3 doses and every 8 wk thereafter for 56 wk (N=207) Placebo (N=206)	– NPS – Nasal congestion – SNOT-22 – UPSIT – Loss of smell – Time to first surgery – OCS use – LMS (CT) – ACQ-6 – Adverse events – Biomarkers: Blood eosinophils	– Improvement in NPS, nasal congestion – Late improvement Loss of smell and SNOT-22 – No improvement: surgery, LMS (CT), OCS use – Improvement in ACQ-6 – No differences in adverse events – Reduction in blood eosinophils
Tversky et al, 2021 [69] RCT	N=24 CRSwNP Previous polypectomy	Benralizumab 30 mg every 4 wk for 20 wk (N=12) Placebo (N=12)	– NPS – Nasal congestion – SNOT-22 – Loss of smell – UPSIT – LMS (CT) – Adverse events	– Improvement in NPS, nasal congestion, SNOT-22 and LMS (CT) – No improvement in UPSIT – No differences in adverse events
Canonica et al, 2022 [70] RCT	ANDHI: N=153, asma y CRSwNP	Benralizumab 30 mg every 4 wk for 24 wk (N=96) Placebo (N=57)	– SNOT-22 – SGRQ – FEV_1 – ACQ-6	– Improvement in SNOT-22 – Improvement in asthma parameters
Bagnasco et al, 2020 [84] Real life	N=34	Benralizumab 30 mg every 4 wk for 24 wk	– SNOT-22 – ACT – OCS use – Anosmia – Biomarkers: Blood eosinophils	– Improvement in SNOT-22 and ACT – Reduction in OCS use – Improvement in anosmia in 31% of patients – Reduction in blood eosinophils
Anti–IL-4Rα (IL-4 e IL-13)				
Bachert C et al, 2019 [60] RCT	SINUS 24: N=276 SINUS 52: N=448	SINUS 24: 24 wk – Dupilumab 300 mg SC every 2 wk (N=143) – Placebo (N=133) SINUS 52: – Dupilumab 300 mg SC every 2 wk, for 52 wk (N=150) – Dupilumab 300 mg SC every 2 wk for 24 wk + 300 mg SC every 4 wk for 28 wk (n=145) – Placebo (N=133)	– NPS – Nasal congestion – Loss of smell – SNOT-22 – VAS-CRS – UPSIT – LMS (CT) – ACQ-6 – FEV_1 – OCS use – Indication for ESS – Blood biomarkers – Nasal biomarkers	– Improvement in both studies (week 24 and 52): – NPS – Nasal congestion – Loss of smell – SNOT-22 – VAS-CRS – UPSIT – LMS (CT) – ACQ-6 – FEV_1 – Reduction in ESS – Reduction in OCS use – Reduction in blood biomarkers: total IgE, TARC, eotaxin 3, periostin (NO eosinophils) – Reduction in nasal biomarkers: ECP, total IgE, eotaxin 3, IL-5

(continued)

Table 5. Efficacy and Safety of Biologics in Treatment of Severe Chronic Rhinosinusitis With Nasal Polyps (*continuation*).

Study	CRSwNP	Treatment	Variables	Results
Anti–IL-4Rα (IL-4 e IL-13)				
Bachert et al, 2016 [73] RCT	N=60	Dupilumab 600 mg SC + 300 mg SC every week for 15 wk (N=30) Placebo (N=30)	– NPS – Nasal congestion – Loss of smell – SNOT-22 – VAS-CRS – UPSIT – LMS (CT) – ACQ-6, FEV_1 – Blood biomarkers: eosinophils, total IgE, eotaxin 3, TARC	Improvement: – NPS – Nasal congestion – Loss of smell – SNOT-22 – VAS-CRS – UPSIT – LMS (CT) – ACQ-6, FEV_1 – Reduction in blood biomarkers: total IgE, eotaxin 3, TARC (NO eosinophils)
Nowsheen et al, 2021 [85] Real life	N=29	Dupilumab 300 mg, every 2 wk for 11 mo (3-20 mo)	– NPS – Nasal congestion – Loss of smell	24 patients (82.8%) had complete response, 3 (10.3%) partial response, and 2 (6.9%) no response
Lans et al, 2022 [86] Real life	Baseline: N=131 48 wk: N=26	Dupilumab 300 mg, every 2 wk for 28 wk	– NPS – Loss of smell – SNOT-22 – Sniffin-Stick – LMS (CT) – PNIF – ACT	Improvement: – NPS – Loss of smell – SNOT-22 – Sniffin-Stick – PNIF – LMS (CT) – ACT EPOS 2020 control: – Control: 0% – Partial control: 94% – No control: 6%

Abbreviations: ACQ, Asthma Control Questionnaire; ACT, Asthma Control Test; AQLQ, Asthma Quality of Life Questionnaire; CT, computed tomography; ECP, eosinophilic cationic protein; EPOS, European Position Paper on Rhinosinusitus; EQ-5D, 5-dimension EuroQol; ESS, endoscopic sinus surgery; LMS, Lund-Mackay Score by CT scan; NA, not available; N-ERD, NSAID-exacerbated respiratory disease; NPS, nasal polyp score; OCS, oral corticosteroids; PNIF, peak nasal inspiratory flow; RSOM, Rhinosinusitis Outcome Measure; SC, subcutaneous; SGRQ, St George's Respiratory Questionnaire; SNOT-22, Sino-Nasal Outcome Test 22; TARC, thymus and activation-regulated chemokine; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analogue score; VAS-CRSwNP, VAS chronic rhinosinusitis with nasal polyps.

molecular pathways involved in the pathogenesis of respiratory inflammatory diseases, including asthma and CRSwNP. A nasal biopsy under local anesthesia would make it possible to exclude a tumor and to pheno-endotype CRSwNP by identifying the degree of tissue eosinophilia and other potential type 2 inflammatory biomarkers [59].

1. Efficacy and safety of biologics in treatment of severe CRSwNP

The efficacy and safety profile of biologics in the treatment of severe CRSwNP has been tested in pivotal clinical trials with dupilumab (SINUS) [60], omalizumab (POLYP) [61], mepolizumab (SYNAPSE) [62], and benralizumab (OSTRO) [63] (Table 5). The baseline characteristics of the study populations and the main treatment outcomes from the biologic phase 3 studies are shown in Tables 6 and 7.

– Anti-IgE monoclonal antibodies (omalizumab). Omalizumab is a humanized monoclonal antibody that binds to free IgE and decreases expression of IgE receptors on mast cells, basophils, and dendritic cells by interfering with their activation (Figure 2A) [64]. Omalizumab has been shown to improve nasal symptoms (including loss of smell) and pulmonary symptoms, NPS, QOL (SNOT-22, SF-36, Asthma Quality of Life Questionnaire [AQLQ]), and reduced need for ESS, with a very favorable safety profile [61,65].
– Anti–IL-5/IL-5Rα monoclonal antibodies (mepolizumab, benralizumab, reslizumab). Reslizumab and mepolizumab are humanized monoclonal antibodies against free IL-5, while benralizumab is an antagonist of the IL-5 receptor α subunit (IL-5Rα) (Figure 2B). The efficacy of reslizumab did not differ with respect to sinonasal symptoms [66], and the drug has not been further developed for the treatment of CRSwNP. Patients treated with mepolizumab saw an improvement in their nasal symptoms, including loss of smell, disease severity, NPS, sinus opacification, and QOL (SNOT-22), as well as a reduction in serum inflammatory biomarkers (eosinophils, eosinophilic cationic protein, and IL-5 receptor), the use of SCS, and the need for ESS; however, the improvement in sense of smell measured by the University of Pennsylvania Smell Identification

Test (UPSIT) was minimal [62,67,68]. Benralizumab led to a late improvement in nasal symptoms, including loss of smell, NPS, and SNOT-22 score. However, no improvement was observed in the sense of smell by UPSIT, sinus opacification, time to first ESS, or use of SCS [63,69,70]. Clinical studies of anti–IL-5 monoclonal antibodies have shown an excellent safety profile [71].

– Anti–IL-4Rα monoclonal antibodies (dupilumab). Dupilumab is a human monoclonal antibody that blocks the subunit of the IL-4Rα receptor while inhibiting the activity of the IL-4 and IL-13 pathways (Figure 2C) [72].

Table 6. Characteristics of the Baseline Population in Pivotal Trials With Biologics in the Treatment of Chronic Rhinosinusitis With Nasal Polyps.

Variables	Benralizumab (OSTRO)	Dupilumab (SINUS)	Mepolizumab (SYNAPSE)	Omalizumab (POLYP)
Patients, No.	410	724	407	265
Female sex, No. (%)	147 (36)	287 (40)	143 (35)	94 (35)
Mean NPS (0-8)	6.1	5.9	5.5	6.2
Nasal congestion (0-3)	>2	>2	9 (0-10)	>2
Loss of smell (0-3)	>2	>2	>9 (0-10)	>2
Mean UPSIT (0-40)	83% with <18*	14.0	NA	13.1
Mean VAS-CRSwNP Severity	ND	7.8 (0-10 cm)	9.1 (0-10)	ND
Mean SNOT-22 (0-110)	69	50.9	64	60
LMS (0-24) mean	ND	18.3	ND	ND
≥1 previous ESS, No. (%)	300 (73)	459 (63)	407 (100)	158 (60)
OCS, No. (%)	307 (75)	538 (74)	197 (48)	59 (22)
Mean blood eosinophils/μL	447	430	395	340
Mean total IgE, kU/L	232	229	NA	175
N-ERD, No. (%)	121 (30)	204 (28)	108 (26)	72 (27)
Asthma, No. (%)	278 (68)	428 (59)	289 (71)	151 (57)

*In the OSTRO study, anosmia (UPSIT <18) was observed in 83% of patients.
Abbreviations: ESS, endoscopic sinus surgery; LMS, Lund-Mackay Score by CT scan; NA, not available; ND, not done; N-ERD, NSAID-exacerbated respiratory disease; NPS, nasal polyp score; OCS, oral corticosteroids; SNOT-22, Sinonasal Outcome Test 22; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog score; VAS-CRSwNP, VAS chronic rhinosinusitis with nasal polyps.

Table 7. Efficacy of Biological Therapy on the Variables of Chronic Rhinosinusitis With Nasal Polyps and Level of Evidence-Based Medicine.

	Omalizumab 24 wk [61]	Dupilumab 52 wk [60]	Mepolizumab 52 wk [62]	Benralizumab 40 wk [63]
Mean reduction in nasal polyp size (0-8)	–1.3	–2.3	–0.7	–0.6
Mean reduction in nasal congestion (0-3)	–0.5	–0.9	–3.1 cm (0-10)	–0.7
Mean reduction in total sinonasal symptoms (0-9)	–2.0 (0-12)	–2.4 (0-9)	3.1 (0-10)	NA
Mean reduction in loss of smell (0-3)	–0.4	–1.0	–0.4 (0-10)	–0.2
Mean improvement in UPSIT (0-40)	+3.8	+10.5	+0.4	NS
Mean SNOT-22 improvement (0-110)[a]	–15.6	–19.1	–16.5	–5.2 (NS)
Mean reduction in LMS (0-24)	–0.2	–7.0	N/A	–0.9 (NS)
Reduction in ESS (%)	–84	–83	–57	–10
Reduction in OCS (%)	–63	–74	–42	NA
Adverse events vs placebo	NS	NS	NS	NS
Level of evidence-based medicine	Ia	Ia	Ia	Ia

Abbreviations: ESS, endoscopic sinus surgery; LMS, Lund-Mackay Score by CT scan; NA, not available; NPS, nasal polyp score; NS, nonsignificant; OCS, oral corticosteroids; SNOT-22, Sino-Nasal Outcome Test 22; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog score.
[a]SNOT-22: minimal clinically important difference >8.9.

It has been shown to improve nasal symptoms, with a fast and persistent effect on loss of smell, NPS, SNOT-22 score, and disease severity. It also led to a rapid and sustained improvement in sense of smell according to UPSIT, sinus opacification, asthma control, and lung function in asthma patients, as well as reduced use of SCS and need for ESS [60,73-76]. In patients with N-ERD, dupilumab led to a greater degree of improvement in the SNOT-22 score, nasal congestion, total symptom score, and peak nasal inspiratory flow than in patients without N-ERD [77]. The frequency of adverse effects was similar in the dupilumab and placebo groups [60].

2. Meta-analyses and indirect comparisons of biologics in CRSwNP

Several network meta-analyses in patients with severe CRSwNP assess direct comparisons between biologics (omalizumab, mepolizumab, dupilumab, and benralizumab) and placebo and make indirect comparisons between the different biologics [78-81]. These meta-analyses show biologics to be superior to placebo for reducing NPS, the need for ESS, and the use of SCS and to improve nasal obstruction, loss of smell, and QOL (SNOT-22). The 3 biologics approved for treatment of the CRSwNP (dupilumab, mepolizumab, and omalizumab) were superior to placebo for improvement in loss of smell. In addition, dupilumab is associated with an early and sustained improvement in smell [78-81].

Indirect comparisons have suggested that dupilumab could present a more marked effect in some efficacy outcomes, with faster and persistent improvement in loss of smell [78-81]. However, the studies are exploratory analyses based on a limited number of studies and with a high percentage of discontinuations and missing data, as well as heterogeneity in both the populations studied and the methodology used. Head-to-head clinical trials are needed to compare efficacy and safety among biologics in severe CRSwNP and thus conclusively establish whether there are significant differences between them in both efficacy and safety.

3. Treatments with biologics (real-life studies) (Table 7)

The main biologics used for the treatment of CRSwNP are omalizumab, mepolizumab, benralizumab, and dupilumab.

- Omalizumab. A study conducted in patients with severe asthma and CRSwNP treated with omalizumab reported an improvement in nasal symptoms, disease severity, asthma exacerbations, and sinus opacification, whereas no significant reduction in NPS was observed [82].
- Mepolizumab. A study in severe asthma and CRSwNP treated with mepolizumab showed an improvement in NPS and the SNOT-22 score and a reduction in blood and tissue eosinophils. However, no reduction in FeNO was reported [83].
- Benralizumab. A study conducted in severe asthma and CRSwNP treated with benralizumab found a reduction in the SNOT-22 score. The study showed a 31% reduction in patients with anosmia (total loss of smell) [84].
- Dupilumab. A study conducted in patients with CRSwNP treated with dupilumab reported an improvement in

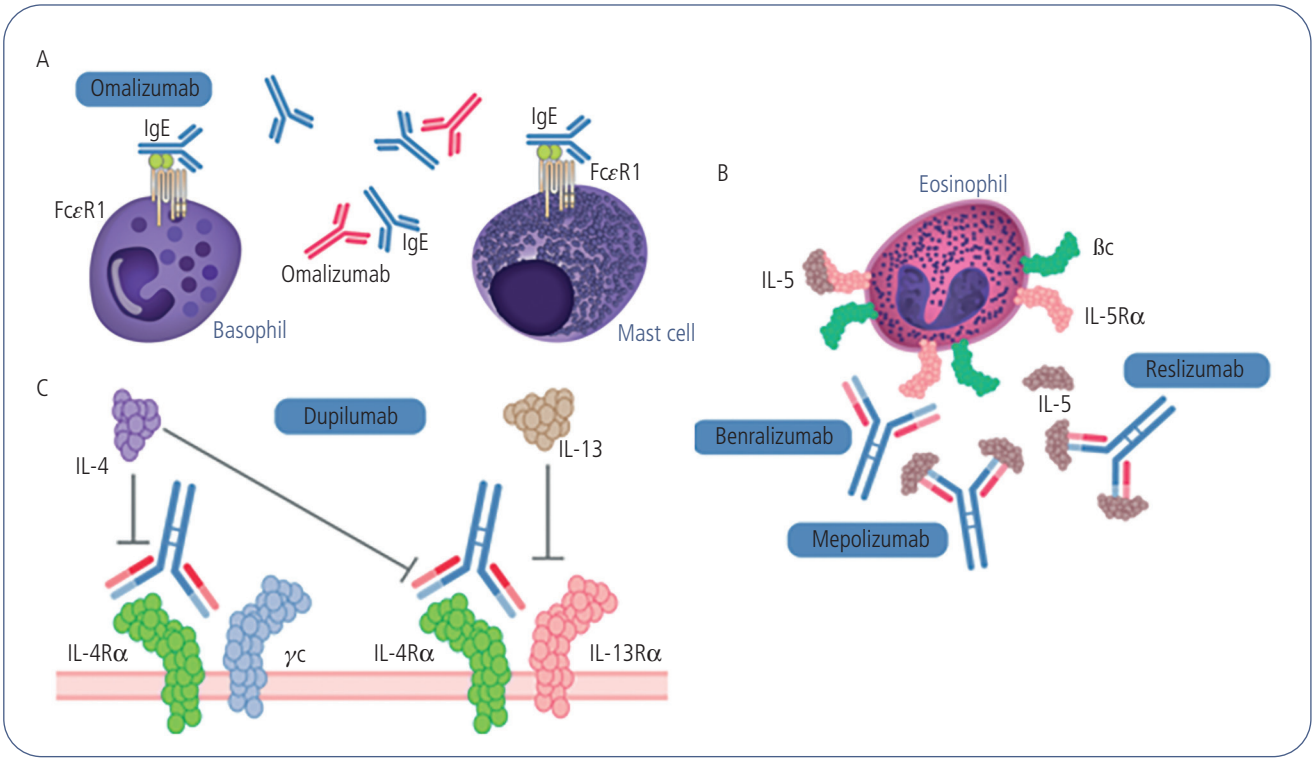

Figure 2. Mechanisms of action of biologics in chronic rinosinusitis with nasal polyps. A, Humanized anti-IgE monoclonal antibody (omalizumab). B, Humanized anti–IL-5 (mepolizumab and reslizumab) and anti–IL-5Rα (benralizumab) monoclonal antibodies. C, Human anti–IL-4Rα monoclonal antibody (dupilumab).

nasal symptoms, including anosmia [85]. Elsewhere, dupilumab was shown to improve efficacy outcomes, including sense of smell. According to the EPOS 2020 control criteria, disease was not considered controlled in any cases (partially controlled in 94% and uncontrolled in 6%).

4. Other comparisons between biologics

A study carried out in patients with severe asthma and CRSwNP treated with anti-IgE, anti–IL-5Rα, and anti–IL-4Rα biologics revealed an improvement in the SNOT-22 score which was higher in the group treated with anti-IL-4Rα than in those treated with anti-IgE and anti–IL-5Rα agents [87]. Nasal and total symptoms improved with anti–IL-5Rα and anti–IL-4Rα agents, but not with anti-IgE agents. The conclusion was that the improvement in efficacy was more favorable in the group treated with anti–IL-4Rα agents.

A study of CRSwNP patients treated with omalizumab, mepolizumab, or benralizumab, showed mepolizumab to be the most successful agent (79%), followed by omalizumab (50%), and benralizumab (50%) [88]. A strong improvement in the sense of smell was observed in patients treated with mepolizumab (29%), followed by benralizumab (17%) and omalizumab (13%).

Finally, a study conducted in severe asthma and CRSwNP treated with omalizumab, mepolizumab, reslizumab, or benralizumab showed that 2 out of every 5 patients presented a subjective improvement in the sense of smell, although anosmia remained unchanged in 60% of patients, with no significant differences between biologics [89].

5. Criteria for indicating biologics

Several consensus guidelines (EUFOREA 2019/2021 and EPOS 2020) have been published on the indication of and response to biologics in the treatment of severe CRSwNP [1,37,90]. Following these international consensus guidelines, the current POLINA guideline proposes modified criteria for the indication of biologics in severe CRSwNP (Figure 3). Biologics would be indicated in "severe bilateral CRSwNP with at least 1 previous ESS" (ESS >6 months) with 1 additional criterion being as follows: presence of type 2 inflammation (high tissue and/or blood eosinophilia or high serum total IgE), severe loss of smell (by smell test or VAS), need for SCS (≥2 short courses from 5 days at a dose of 0.5-1 mg/kg/d) in the last year or contraindication for SCS, or concomitant asthma and/or N-ERD treated with inhaled therapy. In this framework, severe CRSwNP was defined as a VAS >7 cm and/or SNOT-22 >50, whereas ESS should include the opening of the paranasal sinuses (not only nasal polypectomy).

6. Response criteria for biologics

The current POLINA guideline recommends assessment of response to biologics at both 6 and 12 months. Biologic treatment of CRSwNP should be continued if the disease is controlled or partially controlled and accepted by the patient. When the physician and/or the patient considers the disease is uncontrolled, the biologic should be discontinued and a short course of SCS or even ESS/revision surgery is recommended.

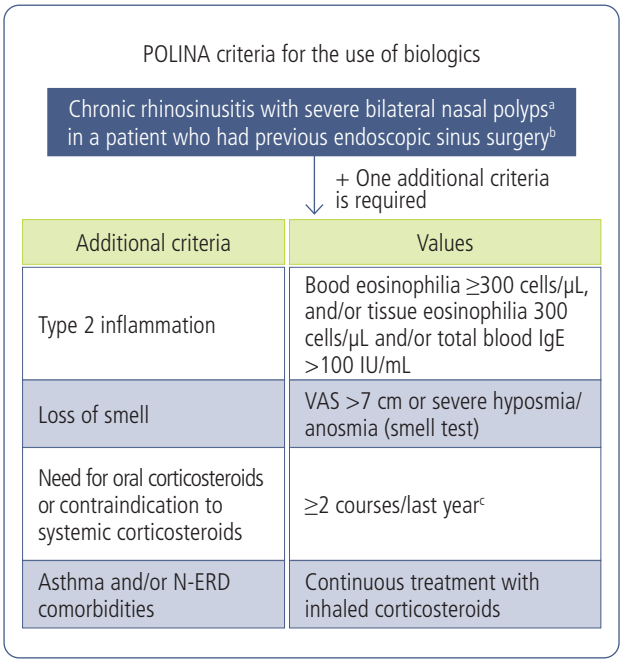

Figure 3. POLINA criteria for the use of biologics. VAS indicates visual analog scale; SNOT-22, Sino-Nasal Outcome Test 22; HPF, high-power field; N-ERD, NSAID-exacerbated anti-inflammatory drugs; VAS, visual analog score.
[a]VAS >7 cm and/or SNOT-22 >50.
[B]Opening of affected paranasal sinuses >6 months.
[c]Short courses from 5 days at a dose of 0.5-1 mg/kg/d.

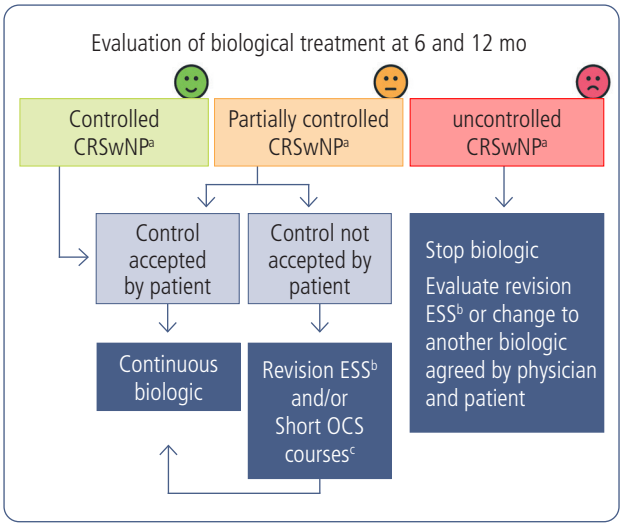

Figure 4. Evaluation of biological treatment for CRSwNP at 6 and 12 months. CRSwNP indicates chronic rhinosinusitis with nasal polyps; ESS, endoscopic sinus surgery; OCS, oral corticosteroid.
[a]See control criteria (Table 2).
[b]Endoscopic sinus surgery with opening of affected paranasal sinuses.
[c]Oral corticosteroids for 5 days at a dose of 0.5-1 mg/kg/d.

In addition, switching from one biologic to another based on control criteria could be evaluated according to pheno-endotyping and agreed upon by both physician and patient (decision-making) (Figure 4).

Unmet needs in CRSwNP

- To define clinical predictors of poor disease control and how this affects the decision of whether treatment should be with biologics or surgery.
- To conduct direct comparative studies on the efficacy and safety of the different biologics.
- To determine the accuracy of biomarkers for assessing response to biologics.
- To conduct studies to determine criteria to stop the use of or switching between biologics.

Conclusions

Patients with CRSwNP and comorbid asthma/N-ERD, as well as those with high corticosteroid use and/or history of sinus surgery, have more severe disease and associated sinonasal symptom burden and are a difficult-to-treat population under the existing management paradigm.

Shared clinician-patient decision making and communication, patient education, and a multidisciplinary strategy may all provide solutions to this major unmet need in CRSwNP.

The role of biologics in the treatment paradigm requires consideration of multiple factors that have yet to be clearly established, for example, identifying the most appropriate patients for biologic therapy while considering long-term safety and cost-effectiveness in the context of patient preferences and goals.

CRSwNP is a burdensome condition in which a high percentage of patients have uncontrolled disease, especially those with comorbid asthma/N-ERD. These patients frequently require corticosteroids and/or sinus surgery, have more severe disease, and represent a difficult-to-treat population under the existing management paradigm.

Shared decision-making, good patient–clinician communication, patient education, and a multidisciplinary strategy may provide solutions to this major unmet need in CRSwNP.

The POLINA consensus is high-quality, evidence-based clinical guideline that has been externally evaluated and may be useful to clinicians attempting to improve the management of CRSwNP.

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Conflicts of Interest

I Alobid has received honoraria for consultancy and conferences from Viatris, Roche, Sanofi, GSK, MSD, Menarini, Salvat, Galensus Health, Olympus, and Novartis.

C Colás has received honoraria for consultancy and conferences from Novartis, GSK, Sanofi, Viatris, Chiesi, MSD, Takeda, Roxall, and Themo Fisher.

JA Castillo has received research grants from AstraZeneca, Boehringer-Ingelheim, GSK, MSD, and Uriach. He has also attended speaker bureaus and/or advisory boards for ALK, AstraZeneca, GSK, Novartis, and Sanofi-Genzyme.

E Arismendi has received honoraria for consultancy and conferences from AstraZeneca, GSK, MSD, Novartis, and Sanofi-Genzyme.

J Sastre has received honoraria for consultancy and conferences from Sanofi, GSK, MSD, Mundipharma, ALK, and Novartis.

A del Cuvillo has received honoraria for consultancy and conferences from MSD, Sanofi, GSK, Menarini, FAES Pharma, Alk Abello, Astra Zeneca, Novartis, Viatris, Uriach, UCB Pharma, and TEVA.

J Mullol is a member of national and international advisory boards and has received speaker fees or funding for clinical trials and research projects from AstraZeneca, Genentech, GSK, Glenmark, Menarini, Mitsubishi-Tanabe, MSD, NOUCOR/Uriach Group, Novartis, Proctor & Gamble, Regeneron Pharmaceuticals Inc., Sanofi-Genzyme, UCB Pharma, and Viatris/MEDA Pharma.

A Gómez-Outes declares that he has no conflicts of interest.

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