

# Biologics: A Revolutionary Treatment To Root Out Chronic Sinusitis With Nasal Polyps

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## Abstract

Chronic rhinosinusitis (CRS) is an inflammatory condition affecting the mucous membranes of the nose and sinuses. [1–5] CRS impacts about 5–12% of people globally, leading to significant costs for health care systems and national economies. [1–4, 6] CRS is categorized into two types: one with nasal polyps (CRSwNP) and one without (CRSsNP). CRSwNP is an immunologically driven chronic inflammatory disease of the mucosa and subepithelial tissue, with specific endotype-oriented immunologic therapies emerging only in the past decade [9–12], while immunotherapies [13–15] have been the standard treatment for a long time for exogenous-allergic nasal mucosal diseases. Biologics are now included in the current guidelines for treating severe uncontrolled CRSwNP. [46-49] While the role of biologics in CRSwNP treatment continues to evolve, the EPOS 2020 guidelines primarily recommend biologics for patients with CRSwNP who are refractory to standard medical therapy and those whose disease persists despite previous surgery.

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## I. Introduction

Chronic rhinosinusitis (CRS) is an inflammatory condition affecting the mucous membranes of the nose and sinuses. [1–5] CRS impacts about 5–12% of people globally, leading to significant costs for health care systems and national economies. [1–4, 6] CRS is categorized into two types: one with nasal polyps (CRSwNP) and one without (CRSsNP). [5–8] CRSwNP, also known as polyposis nasi et sinuum, is characterized by the presence of polypous-hyperplastic tissue in the nasal cavity and/or paranasal sinuses, detectable through endoscopy and/or radiology. CRSwNP is an immunologically driven chronic inflammatory disease of the mucosa and subepithelial tissue, with specific endotype-oriented immunologic therapies emerging only in the past decade [9–12], while immunotherapies [13–15] have been the standard treatment for a long time for exogenous-allergic nasal mucosal diseases.

## II. Chronic Sinusitis With Nasal Polyp

Chronic rhinosinusitis (CRS) is a prevalent and often crippling condition, significantly affecting patients' quality of life (QoL). [16] CRS can be divided into two main phenotypes based on the presence or absence of nasal polyps. [17,18] Up to 20% of all CRS cases are patients with CRS with nasal polyps (CRSwNP). [19,20] In CRSwNP, the disease is primarily driven by type 2 inflammatory processes in most patients, with asthma or other inflammatory diseases (such as NSAID/aspirin-exacerbated respiratory disease or atopic dermatitis) frequently co-occurring. [21] Managing CRSwNP can be difficult. Standard treatments include nasal irrigation, topical intranasal (INS) or oral corticosteroids (OCS). [17,18]

However, a significant number of patients with persistent or uncontrolled symptoms despite these treatments often need endoscopic sinus surgery (ESS) to eliminate diseased tissue and reestablish the anatomical patency of the affected sinuses. [23,24] Even after ESS, further revision surgeries may be necessary. [25,26] Recently, the advent of biologics that target the type-2 inflammatory processes underlying CRSwNP offers additional treatment options for patients with persistent disease despite traditional therapies.

### **III. Earlier Treatment Strategies**

For patients with CRSwNP, initial medical treatments typically included both topical corticosteroids and nasal saline irrigations. [29] Intranasal corticosteroids can reduce the size of nasal polyps, alleviate sinonasal symptoms, and enhance patient quality of life. [30,31] Oral corticosteroids also help decrease polyp size and improve symptoms but must be used with caution due to their potential for serious systemic side effects. [32]

Antibiotics can be beneficial for managing infectious exacerbations of CRSwNP, but large, randomized trials have not shown significant efficacy in terms of polyp reduction. Patients with severe sinonasal disease or those who do not respond to medical treatment should be assessed for sinus surgery. A retrospective study found that waiting more than 5 years from the initial CRS diagnosis to perform sinus surgery was linked to higher post-operative health care use, compared to surgeries done within 12 months of diagnosis. [33]

Functional endoscopic sinus surgery can alleviate sinonasal symptoms and show improvement in sinus CT scan results indicating reduced inflammation. [34] However, nasal polyps may still recur after surgery, [35] and patients with both CRSwNP and asthma typically require more sinus surgeries on average than those with only CRSwNP. [36] In 2011, the US Food and Drug Administration approved Propel™ implants, which are biodegradable stents that release mometasone over 30 days. [37-39] When placed during sinus surgery, these stents reduced the need for postoperative surgical interventions by 51%, oral corticosteroid use by 40%, and significant nasal polyposis by 46% [40] after one month.

### **IV. Modern Treatment Option: Biologics**

The availability of effective biologics that target the underlying type-2 inflammatory pathways in CRSwNP now provides additional treatment options for patients with refractory or uncontrolled CRSwNP. [42,43] Several agents are approved for use in CRSwNP. Dupilumab is a human monoclonal IgG4 antibody that targets the IL-4R $\alpha$  subunit on the IL-4 and IL-13 receptor complexes, inhibiting IL-4 and IL-13 signaling, which leads to reduced IgE production and eosinophil recruitment. [42,44,45] Omalizumab is a human monoclonal IgG1 antibody that binds to the Fc region of circulating IgE, preventing IgE interaction with mast cells, basophils, and B-cells, thereby reducing IgE production and directly affecting IgE B-cell production. [44]

Mepolizumab, a human monoclonal IgG1 antibody, binds to circulating IL-5, preventing its interaction with the  $\alpha$ -chain on the IL-5 receptor on eosinophils, and subsequently inhibiting eosinophil maturation, recruitment, and survival. [44,45] Biologics are now included in the current guidelines for treating severe uncontrolled CRSwNP. [46-49] While the role of biologics in CRSwNP treatment continues to evolve, the EPOS 2020 guidelines primarily recommend biologics for patients with CRSwNP who are refractory to standard medical therapy and those whose disease persists despite previous ESS. Additionally, biologics can be considered for patients unfit for ESS. [50,51]

EPOS 2022 outlines a self-care approach to CRS, where patients may seek advice from pharmacists and use over-the-counter medications for symptom relief. If CRS symptoms persist after 6–12 weeks, management within primary care should include a specialist referral. The panel agrees and advocates for early referral from primary care for all patients with CRS or suspected CRSwNP, ideally within 6–12 weeks. [50,51] This facilitates earlier endoscopic and/or CT evaluation to confirm CRSwNP and rule out other diagnoses, as well as comprehensive clinical and laboratory assessments to identify the associated inflammatory endotype and clinical phenotype, including relevant comorbidities.

A thorough evaluation of comorbidities is crucial, and consulting a pulmonologist is advised for CRSwNP patients with asthma, as this can impact treatment decisions and outcomes. [52,53] The clinical and laboratory assessment of CRSwNP follows established protocols. [47-49, 50,51] As mentioned earlier, either endoscopy or CT scans may be utilized to confirm CRSwNP. Standard laboratory tests include biomarker assessments to determine endotype and confirm the presence of type 2 inflammation, typically involving total serum IgE and serum eosinophils. Tissue eosinophilia analysis is often conducted on surgical specimens and may not be part of the routine initial evaluation. For patients with concurrent asthma, performing baseline spirometry and the Asthma Control Test (ACT) during the initial specialist assessment and throughout follow-up is beneficial.

In EPOS 2020, evaluating the severity of CRSwNP relies on its impact on overall quality of life, [51] with the Sino-Nasal Outcome Test-22 (SNOT-22) being the most commonly employed assessment tool. [54,55] This questionnaire, comprising 22 items, assesses the severity of physical symptoms (12 questions) and their effect on health-related quality of life (10 questions). Patients rate the severity/impact of each question from none to very severe (scored as 0 to 5), generating a total SNOT-22 score ranging from 0 to 110; scores above 50 indicate severe disease impact. [37,38] When utilized to gauge treatment efficacy, a reduction of 8–9 points is deemed the minimum clinically important difference (MCID) in the SNOT-22 score. [56,57]

## V. When To Consider Using Biologics In Crswnp?

As previously mentioned, prior to the approval of biologics, patients with CRSwNP experiencing persistent polyps despite medication and/or surgery had no therapeutic options, resulting in refractory, uncontrolled CRSwNP. Biologics are now a recommended standard therapy for this subgroup of patients. Biologics are also suggested as a standard treatment for another subgroup of CRSwNP patients who can achieve improved control of their condition with long-term systemic corticosteroid therapy, provided they can tolerate the associated adverse effects. [58]

Important factors to consider regarding the use of biologics may include: [59]

- Evidence indicating type 2 inflammatory polyps (such as eosinophils observed on polyp histology, peripheral blood eosinophilia of  $\geq 0.3 \times 10^9/L$ , or clear systemic steroid responsiveness)
- Significant decline in quality of life (indicated by a SNOT-22 score exceeding 40 points) despite consistent use of intranasal corticosteroids (unless medically unsuitable), prior surgical intervention (if the patient is eligible), and use of systemic corticosteroids for nasal conditions within the past 12 months (unless medically unsuitable)

Additionally:

- Impact of loss of smell (eg, on profession)
- Sleep-disordered breathing
- Comorbid asthma (but severe asthma should be considered for a biologic on its own merit)
- Failed or contraindicated or unavailable trial of aspirin desensitization if patient has AERD
- Steroid side effects/contraindications (reduced bone density, cataract, glaucoma)
- Relative costs of available drugs

Response evaluation should be done first at 16 weeks and second at 1 year. One should consider the continued usage of biologics when there is improved quality of life and there is more than 50% reduced usage of systemic steroid drugs. Also, when symptoms of smell and nasal obstruction improve and there is  $> 2$  change in size of polyp from baseline on Meltzer 8-point bilateral grading system. Lastly, there is reduced impact of comorbidities.

EPOS 2020, states that excellent response is seen when all 5 criterias are met, moderate response when 3-4 criterias, poor response when 1-2 criterias and no response when 1 criterias are met. In case of no response, one should stop biologics.

## VI. Conclusion

The advent of biologics holds promise for revolutionizing the current management of patients dealing with persistent CRSwNP. Biologics should be contemplated for individuals experiencing ongoing, unmanageable symptoms despite undergoing thorough ESS (or in cases where surgery is not advisable). Response to biologic treatment should be evaluated based on established criteria, ideally after a span of 4–6 months, and alternative treatment options should be explored if the response is unsatisfactory. This may involve considering revision surgery or transitioning to a different biologic.

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