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EXPERT OPINION

Multi-Disciplinary Expert Perspective on the Management of Type 2 Inflammation-Driven Severe CRSwNP: A Brief Overview of Pathophysiology and Recent Clinical Insights

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Abstract: Severe chronic rhinosinusitis with nasal polyposis (CRSwNP) is a disabling airway disease that significantly impacts patients' lives through the severity of symptoms, the need for long-term medical treatment and the high risk of recurrence post-surgery. Biological agents targeting type 2 immune responses underlying the pathogenesis of CRSwNP have shown effectiveness in reducing polyp size and eosinophilic infiltrate, and in decreasing the need for additional sinus surgeries. However, despite recent progress in understanding and treating the disease, type 2 inflammation-driven severe CRSwNP continues to pose challenges to clinical management due to several factors such as persistent inflammation, polyp recurrence, heterogeneity of disease, and comorbidities. This article presents the findings of a scientific discussion involving a panel of ear, nose and throat (ENT) specialists and pulmonologists across Sweden and Finland. The discussion aimed to explore current management practices for type 2 inflammation-driven severe CRSwNP in the Nordic region. The main topics examined encompassed screening and referral, measurements of disease control, treatment goals, and future perspectives. The experts emphasized the importance of a collaborative approach in the management of this challenging patient population. The discussion also revealed a need to broaden treatment options for patients with type 2 inflammation-driven CRSwNP and comorbid conditions with shared type 2 pathophysiology. In light of the supporting evidence, a shift in the disease model from the presence of polyps to that of type 2 inflammation may be warranted. Overall, this discussion provides valuable insights for the scientific community and can potentially guide the future management of CRSwNP.

Keywords: chronic rhinosinusitis, type 2 immunity, surgery, biological therapy, Nordic countries, collaboration

Introduction

Chronic rhinosinusitis (CRS) is defined by the presence of sinonasal symptoms such as nasal blockage/obstruction/congestion or nasal discharge, persisting for 12 weeks or more.[1] CRS is a clinical syndrome comprising a group of disorders with different phenotypes and degrees of severity.[2] Phenotypically, it is divided into CRS with nasal polyps (CRSwNP) and without (CRSsNP).[1] CRS has a multi-factorial etiology comprising alterations in mucociliary clearance, epithelial cell barrier abnormalities, and tissue remodeling.[3] The main pathomechanisms in CRS appear to involve dysfunctional interactions between the host and environmental stressors at the sinonasal mucosa, arising from an interplay between genetic/epigenetic factors and exposure to infectious agents or airborne irritants.[4]

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Around one in ten people are thought to suffer from CRS in Europe,[5] although estimates vary across geographical regions.[6] CRSwNP accounts for up to 20% of all CRS cases and is more debilitating than the phenotype without nasal polyposis.[7] Epidemiological studies such as the large, multi-center Global Allergy and Asthma Network of Excellence (GA2LEN) survey[8] revealed a higher prevalence of CRS in asthmatic patients compared to the general population.[9] A 2020 systematic literature review[10] found that asthma (5–56% of patients), allergy (12–77%), and allergic rhinitis (17–76%) were the most reported comorbidities in CRSwNP patients. Asthma in the presence of nasal polyps is harder to control and more prone to exacerbations,[7] and poor symptom control in severely asthmatic patients is correlated to high computerized tomography (CT) scores of the sinuses.[11] Severe CRSwNP is defined as bilateral CRSwNP with a nasal polyp score of at least 4 of 8 points and persistent symptoms despite long-term intranasal corticosteroids (INCS) with need for add-on treatment.[12] Severe CRSwNP poses a considerable burden on patients' lives as well as the healthcare systems.[12]

Dysregulated immunity plays a major role in the pathogenesis of severe CRS.[13] Three types of innate and adaptive immunity have been described.[14,15] Type 1 immunity targets viruses, protozoa, and intercellular bacteria and involves the interferon g-producing group 1 innate lymphoid cells (ILC1), natural killer cells and T-helper (Th) 1 cells.[14] Type 2 immunity has originally evolved to defend humans against helminth parasites and is mediated by ILC2, macrophages, mast cells, basophils, and eosinophils, which produce cytokines such as interleukin (IL)-4, IL-5, and IL-13.[15] Type 2 cytokines have specific roles within the inflammatory pathway, with IL-5 primarily promoting eosinophil differentiation and recruitment to the sites of allergic inflammation,[16,17] while IL-4 and IL-13 are responsible for B-cell isotype class switching to immunoglobulin E (Ig E) production, immune cell trafficking to tissue, and driving and sustaining the Th2 response.[18] Finally, type 3 immunity protects against extracellular bacteria and fungi, and is mediated by ILC3, Th17 and Th22 cells producing cytokines IL-17, IL-22, and IL-23.[14]

Dysregulated types 1 and 3 immune responses mediate autoimmune diseases, while type 2 responses can cause allergic diseases.[14] In CRS, the type 2 (Th2) endotype is associated with eosinophilic inflammation and forms the majority of CRSwNP cases in the Western world.[19] Type 2 inflammation-driven CRSwNP typically co-occurs with asthma and/or non-steroidal drug-exacerbated respiratory disease (NERD),[12] also referred to as aspirin-exacerbated respiratory disease or Samter's triad.[1] Type 2 inflammation is a major feature of CRSwNP and allergic rhinitis, and the most common and studied endotype in upper airway diseases.[20] Comorbid conditions such as eosinophilic esophagitis, chronic otitis media, and atopic dermatitis share type 2 inflammatory pathways with CRSwNP and asthma, and therefore may be simultaneously targeted for treatment.[15] The other two types of immune responses can also be implicated in the pathogenesis of CRS: the type 1 (Th1) endotype is characterized by non-eosinophilic inflammation, whereas the type 3 (Th17) endotype is found in both eosinophilic and non-eosinophilic cases of CRS.[19]

The recent interest in biomarker research, fueled by the advent of biological therapies,[12] has enabled the identification of several different CRS clusters with specific inflammatory signatures, highlighting a preponderance of Th2 inflammatory profiles.[21] Among these, the group with high IL-5 levels had an almost exclusive nasal polyp phenotype with strongly increased asthma prevalence.[21] Population studies have also revealed that, while the Th2-driven CRSwNP endotype is present in approximately 80% of Caucasian patients, a Th1/Th17 inflammatory profile is dominant in those from Asia.[22–24] However, on an individual basis, immunological disease profiles are likely to be more complex due to the heterogeneous nature of inflammatory disease in CRS[21] and the potential overlap between different endotypes.[9] Furthermore, deciphering the underlying immune pathways has shifted the current understanding of CRS, with experts calling for a switch from an organ-based to a molecular-based classification.[13]

The heterogeneous nature of CRSwNP means that patients present with various clinical features and may respond to treatment differently.[25] The management of severe CRSwNP is therefore complex and challenging.[12] According to the European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) 2020 guidelines, INCS and nasal saline irrigation are the mainstay of treatment in CRS.[1] However, international guidelines differ with regards to the long-term use of oral corticosteroids (OCS) and antibiotics due to concerns regarding side effects.[1]

Endoscopic sinus surgery (ESS) is a common treatment option for CRSwNP patients who do not respond to conservative medical therapy[1] but is associated with high polyp recurrence rates of up to 40% at 2–3 years.[26] Repeated surgical interventions, long-term exposure to corticosteroid medication, and a lack of efficacious therapies to maintain disease control post-surgery are all challenges in the management of patients with severe CRSwNP.[12] Furthermore, patients with a pure or

mixed type 2 CRS endotype appear to be more resistant to standard therapies, and show higher recurrence rates, than those with pure type 1 or type 3 endotypes.[1]

Biological therapies targeting type 2 inflammatory mediators offer a promising new strategy for achieving therapeutic benefits in this difficult-to-treat patient population, moving the field one step closer to precision medicine.[13,17,20,27] Targeted therapies can also address conditions with shared type 2 pathophysiology that frequently co-occur with CRSwNP.[15] For example, IL-5 blocker mepolizumab has proven effective in CRSwNP and asthma with high eosinophil levels in sputum, whereas dual targeting of IL-4 and IL-13 by monoclonal antibody dupilumab has shown efficacy across CRSwNP, asthma, eosinophilic esophagitis, and atopic dermatitis,[15] and recently in uncontrolled chronic obstructive pulmonary disease with high eosinophil counts.[28] Currently, four biologics targeting type 2 inflammatory mechanisms have been approved for the treatment of CRSwNP: omalizumab (anti-IgE), mepolizumab (anti-IL-5), benralizumab (anti-IL-5R), and dupilumab.[29] Data are emerging on the real-world experience with biologics in CRSwNP: in a Finnish cohort of patients with asthma and concomitant CRS, treatment with anti-IgE and/or anti-IL-5/5R biologics reduced the overall need for OCS, even though discontinuation rates remained high.[30]

Challenges of CRSwNP Management in the Nordic Countries

Severe CRSwNP continues to pose a considerable burden in the Nordic countries. The prevalence of CRSwNP was estimated at 2.7% in Sweden[31] and 4.3% in Finland.[32] In Sweden, 46,000 surgical interventions were performed on 31,480 patients due to CRSwNP between January 1987 to December 2015.[33] Between 2012 and 2019 in Finland, the prevalence of CRSwNP rose from 602.2 to 856.7 patients per 100,000 people.[34] In this patient group, presence of severe asthma significantly increased the probability of receiving systemic corticosteroids and undergoing ESS.[34] A large hospital registry study in Finland[35] found that CRSwNP was associated with a disproportionate number of hospital visits (10/year, compared with 7 for asthma patients) despite comprising a relatively small proportion of the total number of diagnoses (7 patients at tertiary care per 100,000 inhabitants/year, vs 70 with asthma). Taken together, these findings signal an urgent need for improved management of CRSwNP in Finland.[34]

Towards a Collaborative Approach in Severe CRSwNP

In light of the common pathophysiological elements of upper and lower airway disease and their frequent co-occurrence and anatomic continuity, the umbrella term of "global" or "united" airway disease has been suggested.[36,37] A key clinical implication of this concept is the need for a unified management approach, in which the patient is examined holistically and treatment decisions are taken jointly between ear, nose and throat (ENT) consultants and pulmonologists.[36] The importance of a multi-disciplinary approach has been underscored on a global scale by the European Forum for Research and Education in Allergy and Airway Diseases (EUFOREA)[38,39] and adapted by expert panels for various geographical regions, including Northern Europe[36] and the Gulf countries.[2]

Publication Rationale and Objectives

Despite the rise in initiatives aiming to improve collaborative working, gaps in awareness and implementation remain.[2,36] The present article aims to address some of these gaps by updating the medical community on the latest clinical insights and guidance in the management of severe CRSwNP, identifying areas of consensus and future directions of development, and highlighting the importance of a harmonized approach to patient care. The paper summarizes the findings of a multi-disciplinary taskforce discussing a number of key themes in CRSwNP, including: patient screening and referral; management of exacerbations; potential biomarkers and patient endotyping; measurements of disease control; treatment goals, pathways and guidelines.

Methodology

During an advisory board meeting held in May 2023, a panel of ENT consultants/surgeons and pulmonologists (with some specializing in asthma and allergology) working in university or tertiary care settings across Finland and Sweden shared their perspectives on the management of type 2 inflammation-driven severe CRSwNP. The objective of this taskforce was to present the perspective of the Nordic region, reflecting best practices from Finland and Sweden.

A set of questions was used to guide the discussion, and key themes pertaining to the screening, referral, and treatment pathways of patients with severe CRSwNP were identified. The collective perspective of the expert group is summarized below.

Discussion and Expert Opinion

How Do You Assess Your CRSwNP Patient and How Does This Affect Treatment Choice?

Around 46% of patients with CRSwNP are estimated to have undergone ESS in Europe, with a mean number of 1.4–2.98 procedures in those with concurrent asthma.[10] Surgery is associated with high recurrence rates in medically recalcitrant CRSwNP.[26] Patients with NERD are at a higher risk of uncontrolled CRSwNP than those without NERD, as measured by revision ESS and/or rescue therapy following surgery.[40]

In alignment with the EPOS guidelines,[1] patients with severe CRSwNP from Finland and Sweden who are candidates for ESS typically undergo screening for blood eosinophilia, total IgE and specific IgE levels for the most common allergens, as well as a polyp biopsy to assess tissue eosinophilia. The ENT surgeon will also inquire into the patient's asthma symptoms and any signs of non-steroidal anti-inflammatory (NSAID) hypersensitivity. A nasal polyp score and Sino-Nasal Outcome Test (SNOT)-22 questionnaire are administered to assess the patient's pre-operative symptom severity. The patient will also be questioned about altered sense of smell and taste. A CT scan of the sinuses can be used to study the polyps and count Lund-Mackay score. According to the EPOS 2020 position paper, magnetic resonance imaging can aid greatly in the diagnosis of concomitant orbital and intracranial complications, which have been reported in both children and adults with CRS.[1] These assessments underpin therapeutic decision making, eg, proceeding with extensive or partial surgery targeting the paranasal sinuses. If seen by a pulmonologist, patients are asked about their CRSwNP and asthma symptoms, changes in their ability to smell and taste, and prior use of INCS and OCS. Breathing issues are investigated and a fractional exhaled nitric oxide (FeNO) test may be conducted at this stage to assess airway inflammation.

Patient-reported quality of life (QoL) is valuable for informing treatment decisions and is also useful in follow-up when implemented systematically. Changes to or loss of smell, which are linked to a short-lived effect of corticosteroids and poor surgery outcomes, constitute a criterion for initiation of biological treatment according to the EPOS guidelines.[1]

Most cases of severe CRSwNP present with eosinophilic polyps, which are linked to a high risk of recurrence.[1] Severely eosinophilic patients tend to have comorbid asthma and NSAID hypersensitivity, which share with CRSwNP elements of inflammation-driven pathophysiology. High baseline eosinophilia, together with asthma and NERD, have been associated with a 4.5-fold higher recurrence risk for nasal polyps after surgery.[41] Nonetheless, some CRS patients may present with eosinophilic upper and lower airway inflammation without polyps. Therefore, a more inclusive term for characterizing the disease may be eosinophilic chronic rhinosinusitis (eCRS), which denotes type 2 inflammation whether polyps are present or not.[42] A diagnosis of eCRS is confirmed upon examination of a biopsy specimen or resected tissue under a microscope at high-power field (HPF) of 400x.[1,42] The threshold number of 10 tissue eosinophils/HPF is recommended by the EPOS 2020 guidelines for a final diagnosis of eCRS.[1] In practice, eosinophilia is confirmed where tissue eosinophils comprise more than 30% of the inflammatory cells present; in clinical studies, a cutoff value of 27% was found to predict polyp recurrence with 96.7% sensitivity and 92.5% specificity.[1,43] Patients who have undergone biological therapy display little or no polyp eosinophilia. Nevertheless, if there are any concerns regarding eosinophilic inflammation, a nasal biopsy can be easily performed in office, under local anesthetic.

There is no harmonized approach to the management of severe CRSwNP across the Nordic countries, and clinical guidelines reveal a lack of consensus on when to offer surgical treatment or how extensive it should be, and when to initiate biologics.[44] In Finland, local guidelines[45] require extensive operative intervention (ie, total ethmoidectomy) before considering biological treatment. In Sweden, a comprehensive work-up of patients with recurrent CRSwNP with previous surgery is recommended only when their disease is advanced enough to warrant biological treatment;[44] in these scenarios, the tests performed follow the EPOS 2020 guidelines.[1]

Does Exacerbation of CRSwNP Symptoms Differ from Polyp Recurrence?

Defined by EPOS 2020 as a temporary aggravation of symptoms,[1] acute exacerbations typically occur after treatment with systemic corticosteroids and/or antibiotics.[46] Acute CRSwNP exacerbations have been associated with an average 7.83-point increase in SNOT-22[47] and pose a considerable burden on patients' daily lives as well as the healthcare systems.[46]

Exacerbations in CRSwNP are triggered by viral or bacterial infections, but the clinical backdrop is often more complex.[46] The group was in consensus on the difference between symptom exacerbation and polyp recurrence: the former is typically caused by post-viral inflammation and requires short-term treatment, where the latter displays a slowly increasing symptom burden, which requires escalation of long-term treatment.

Are There Factors That Can Predict Exacerbation of CRSwNP and Recurrence of Polyps?

Predictive factors for CRSwNP exacerbations include: eosinophilia, co-occurrence of asthma, NSAID intolerance, recurrent need for OCS, and non-compliance with standard treatment. A large number of prior surgeries is indicative of poor disease control and will likely require a more aggressive post-operative intervention, eg, using budesonide in nasal irrigation, etc. However, the group highlighted the large degree of inter-patient variability with regards to surgery outcomes in this population.

What Collaboration Exists Today Between Pulmonologists and ENT Specialists for Patients with Upper and Lower Airway Diseases? To What Extent are Lower Airway Symptoms Assessed in CRSwNP and How Does That Influence the Choice of Treatment?

Experts emphasized that, in cases of lower airway involvement, collaboration and communication between ENT specialists and pulmonologists are essential. Physicians should assess the available management options jointly with the patient and should communicate effectively to address patients' expectations, particularly for those at risk of disease recurrence.[36,38] Rhinologists may want to explain that sinus surgery is needed to widen the sinus openings and allow topical steroid and nasal rinsing to act effectively. However, they could also highlight that surgery will not cure the ongoing eosinophilic inflammation and that, while the majority of patients do benefit from ESS, close post-operative monitoring is required in some cases. The option of biological therapy could also be discussed at this stage, even if there are plans to operate.

Asthma patients suffering from comorbid severe polyps and exacerbations who present to a pulmonologist are typically referred to the ENT specialist to provide a second opinion and to check CRS staging for later evaluations. In patients with severe asthma and less severe comorbid CRS, biological treatment targeting lower airway disease may be initiated before ENT referral, if allowed by local reimbursement policies.

The benefit of a multi-disciplinary approach to treating both upper and lower airway disease was a recurring theme of the discussion. A compelling illustration of the collaborative model of care is the LUAM (Lund United Airway Clinic) initiative at Lund University Hospital, Sweden, where patients receive joint appointments with the ENT and pulmonology consultants in the same room. As well as taking part in various assessments, clinicians discuss and jointly coordinate a whole-person evaluation and plan ahead of surgery or biological therapy. Started early 2023, the initiative has gained momentum, with positive feedback from participating physicians and patients. Experts agreed this type of care model can be highly beneficial for some patients, enabling them to ask questions and receive synchronized answers. However, it may not fit all real-life scenarios, and time-effectiveness considerations may be a priority in individual cases.

In Finland, pulmonologists and ENT consultants work in close cooperation, with collaborative models of care established within university hospitals in Helsinki, Turku, and Tampere, among other university hospitals.

Is It Possible to Endotype CRSwNP Patients Using Biomarkers to Choose the Best Treatment? What Information or Patient Data Do You Need When Selecting Treatment?

The EPOS 2020 guidelines observe that progress in CRS endotyping over the last decade has led to management strategies based on endotyping and phenotyping.[1] Patient subtyping is expected to become increasingly important for

decision-making as more biomarkers are identified and validated in CRSwNP. Currently, blood eosinophils, FeNO, IgE (total and allergen-specific), and leukocyte counts are being used to subtype patients.

With the advent of biological therapies and the improved understanding of type 2 inflammation as shared pathophysiological mechanism in CRSwNP and asthma, it has become possible to assess the inflammatory endotype of disease and target treatment accordingly.[20] Recent pathophysiological studies[48] have implicated a number of other pro-inflammatory cytokines, such as IL-25 and IL-33. As ever, these results must be interpreted cautiously as correlation with actual treatment response may be poor. Ideally, biomarkers can be used not only to predict treatment response but also to evaluate response and predict long-term outcomes. However, experts advised against narrowing the patient selection criteria too much as it can potentially restrict access to targeted treatment in those who would otherwise benefit from it. Rather, clinicians should consider a patient's clinical picture holistically, while being aware of individual variations.

What is the Current Goal for the Treatment of Severe CRSwNP and How Do You Measure Disease Control?

The EPOS 2020 guidelines define control in CRS as

> a disease state in which the patients do not have symptoms, or the symptoms do not adversely affect quality of life, if possible combined with a healthy or almost healthy mucosa and only need for local medication.[1]

Evaluating disease control is based on an interplay between patient-reported outcomes and objective measurements of disease progression. While some experts felt patient-reported outcomes are more reflective of the disease status, others stressed the role of objective measurements such as endoscopic scoring systems and Sniffin sticks for anosmia. There was general consensus on the suitability of the SNOT-22 symptom severity questionnaire for assessing disease control, with a threshold of 20 and 25 marking the patients' and clinicians' perception of control, respectively.[49] Experts observed that recovery to normal SNOT-22 scores can occur after sinus surgery but gradually worsens over time; a more constant improvement can be obtained with biological therapy.

Overall, it was agreed that a complete set of treatment goals in severe CRSwNP should combine QoL assessments with the endoscopic picture of disease. Treatment goals should also include the SNOT-22 and Asthma Control test scores, biomarkers such as FeNO, and smell testing.

As treatment options for these patients broaden, biological therapies offer the possibility of addressing comorbid conditions such as eosinophilic esophagitis and atopic dermatitis, which share elements of type 2 inflammation with CRSwNP and asthma.[15]

Case Scenario: Challenges in the Management of Severe CRSwNP

Below is a fictional case scenario highlighting the complexity of managing severe CRSwNP in the clinic and the need for a personalized treatment approach.

Patient Case

A 50-year-old female has suffered from moderate-to-severe CRSwNP and asthma for 15 years. She has received regular treatment with INCS, long-acting beta agonists and montelukast for over 10 years.

She usually experiences 2–3 prolonged upper and/or lower airway exacerbations per year after viral infections, with a need for an oral corticosteroid course of about 7 days. During exacerbations, her productivity decreases significantly for 3 weeks, while the benefit provided by the oral corticosteroid lasts for only 2 weeks.

In general, she has difficult symptoms that affect her sleep and everyday life. She suffers from severe nasal obstruction, anosmia, mucus production, wheeze/cough with exercise and during exacerbations. Although she has undergone ESS (polypectomy, middle meatal antrostomy, anterior ethmoidectomy) her nasal polyps have re-grown after 2 years, and her symptoms returned. She is not willing to undergo another operation as she suffered from post-operative bleeding and pain, and she also has an increased risk of bleeding and of hematomas in general.

Summary and Future Outlook

Herein, we have captured the outcomes of a multi-faceted discussion on management practices for severe CRSwNP, which involved a panel of pulmonologists and ENT specialists from the Nordic countries. Alongside expert opinion and best practice recommendations, we have provided an overview of the latest research concepts and data, including the role of type 2 inflammation in the pathophysiology of disease and the importance of targeting specific inflammatory pathways to effectively treat severe CRSwNP. Nevertheless, as an expert opinion piece, this publication reflects the views of its authors based on the current literature and scientific knowledge.

In summary, the group proposed that biological therapeutics are under-utilized and expanding the indications to include CRSwNP for targeted agents will benefit patient outcomes. Surgery is expected to remain a component of the future treatment armamentarium in severe CRSwNP, especially if there are anatomical abnormalities, although the number of revision surgeries is likely to decrease. In this context, it will be essential to find the right combination between surgery and biological therapy so that excess polyp mass can be reduced with surgical interventions, while disease control can be maintained with biologics if initiated shortly after. A better understanding of biomarkers will inform the appropriate selection of biological therapies based on the immunological signature of the disease subtype. A parallel treatment paradigm is seen in rheumatoid arthritis, where chronic inflammation is now controlled first, while surgery is used to treat severe joint deterioration.

From a disease model perspective, a shift in focus from the presence of polyps to that of eosinophilia and eCRS may be warranted; this reflects the growing body of evidence around a role for eosinophilic inflammation in the pathogenesis of severe CRSwNP.

Finally, a key component of the future management of severe CRSwNP will be the collaborative approach to treating global airway disease and associated comorbidities, involving a multi-disciplinary team of rhinologists, pulmonologists and dermatologists, as well as medical students in training.

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