RHINOLOGY REVIEW

Recent advances in chronic rhinosinusitis: pathophysiology, treatments, and outcome measures

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Abstract

This review discusses major developments in chronic rhinosinusitis. The latest papers on prevalence of the disease, the burden for patients and society, the lack of awareness, the development of patient classifications and the consequences for the management of the disease. Our discussion includes major developments in the treatment of the disease with biologics but also their limitations. Recent developments also include evolution in the goals of care, where until recently we were content with control of disease but now start to aim for remission and maybe even cure. To reach that aim we need better definitions of disease, outcomes and biomarkers to predict the optimal moment of intervention in the development of the disease. Time will tell whether earlier intervention can prevent development of the disease and later sequelae.

Key words: chronic rhinosinusitis, control, remission, biologic, pathophysiology, treatment

Introduction

Chronic rhinosinusitis (CRS), often in the form of primary diffuse disease, is a prevalent disease with high impact on patients and society [(1)]. While prevalence numbers for all CRS are estimated to be around 4-5% in Europe [(2, 3)], the prevalence of nasal polyps (CRSwNP) – often a sign of type2 disease – is estimated to be 1-2% (1) and latest Spanish data suggest a prevalence of 0.12% for severe CRSwNP [(4)]. The costs of CRSwNP are to a large extent attributable to presenteeism and absenteeism [(5, 6)], but one should not overlook the strain this disease puts on hospital resources. In a UK database study, it was shown that most CRSwNP patient undergoing surgery would have another one within a decade, especially when having comorbidities such as asthma [(7)]. Despite such increasing evidence showing the burden of this disease, awareness is low, calling for actions like the recently Global CRSwNP Awareness day [(8)].

From phenotypes to endotypes

Discriminating phenotypes in inflammatory upper airway diseases, particularly allergic rhinitis (AR), non-allergic rhinitis (NAR) and CRS seems to be a simple task for otorhinolaryngologists using a patient's history, clinical/endoscopic examination and formal allergy testing, lab findings as well as imaging. However, these conditions are very frequent in the general population and often treated by primary healthcare professionals with a limited spectrum of diagnostic instruments. We all learned in medical school that taking an appropriate history is key in giving the right diagnosis. However, recent scientific advances have shown us how to elevate a standard patient history to maximize predictive accuracy. As a prime example, recent research has reported that combining 9 different symptom severity scores (Total nasal symptoms, obstruction, postnasal drip, rhinorrhoea, nasal itch, sneezing, ocular itch, headache, loss of smell) measured using a visual analogue scale resulted in a highly predictive model that differentiated AR, NAR and CRS [(9)]. Even overlapping phenotypes could be adequately identified highlighting the importance of targeted questions. This also opens a field of research focusing just on symptoms rather than complex tests [(9)].

With the new CRS classification as proposed in the European position paper on Rhinosinusitis and nasal polyps: EPOS2020 [(1)], the field is moving towards more endotype-driven therapy [(10, 11)]. Still, the cornerstone of diagnosis is taking an adequate history and combining this with an appreciation of objective status of the nose and sinuses, either by nasal endoscopy, and/or imaging. Both have their experienced recent developments, and both have their respective advantages and flaws [(12-14)]. Especially in the context of nasal polyps, endoscopic grading systems quantifying the amount of polyp volume and their location into a single digit are known to have their limitations. Often implemented with nasal polyp scores ranging from 0 to 3 or 0 to 4 per side (totalling to [0-6] or [0-8]), these scales have non-linear scoring with distinct flooring and ceiling effects [(12, 14)]. Moreover, a polyp score is a small aspect of the disease; and a systematic review has shown nasal polyp score does not to correlate with patient-reported outcome measures or psychophysical testing of olfaction [(15)]. On the other hand, it is currently

the only way to measure the physical load and burden of polyps, which might be a reflection of disease activity and, as such, might help in managing patient expectations when performing surgery [16]. The grading of nasal polyps and other forms of inflammation is also complicated when choosing treatments based on underlying inflammatory mechanisms [17, 18].

Although we are lacking readily available and diverse biomarkers [19], at least the value of a is increasingly appreciated. As a marker of type-2 disease, BEC helps direct therapy and predict outcomes. In an open label, non-inferiority randomized controlled trial, Deng et al. have shown how tailoring treatment (in this case: with adjusted dose of oral corticosteroids) to the presence of elevated BEC leads to comparable, non-inferior, outcomes when compared to standard of care (OCS) treatment [20]. In this study, a cut-off of 0.37×10^9 cells/L was used, which is relatively high compared to those used in the EPOS2020 document [1] (0.25×10^9 cells/L) and the update from the EPOS/EUFOREA group (0.15×10^9 cells/L) in the context of indicating biological treatment [18]. In the same context, another often mentioned biomarker for type2 disease, serum total immunoglobulin E, seems to have limited added value over BEC [21].
Another somewhat more invasive biomarker is the level of tissue eosinophils from sinonasal tissue (e.g., polyp) biopsies. While most classifications rely on different parameters, tissue eosinophilia is amongst the most important factors and >10 eosinophils/high power field (HPF) is often considered the cut off (EPOS) for type 2 disease. Higher eosinophil levels are associated with disease severity, worse surgical prognosis and require more aggressive treatment. As overlaps of endotypes may occur and clear definitions of subtypes are missing, a stronger focus on recurrence could be made. Based on recurrence after surgery, a higher cut off of 55/HPF was therefore suggested for eosinophilic CRS (eCRS) based on tissue biopsies, leading to fewer diagnoses of eCRS and potentially less "overtreatment" [22]. Nevertheless, the protocol for histopathologic assessment of tissue eosinophilia (i.e. average, maximum) and, also the correct timepoint (biopsies vs surgery) as well as influence of treatments (topical and systemic steroids) are still debated questions [22-26].
Although there is much debate on the determination and cut-offs to be used for tissue eosinophil count, it is a strong predictor of recurrent disease after endoscopic sinus surgery (ESS) [27]. Although it has been argued that in a chronic inflammatory disease, a discussion of recurrence is less accurate than discussing loss of disease control [10]. The same holds true for the paediatric CRS population, where tissue eosinophilia was shown to be a strong predictor of revision surgery [28].

Another 'marker' associated with type2 CRS is the presence of asthma (especially late-onset eosinophilic asthma) [29]. Unfortunately, treatment strategies of CRS and asthma are often siloed within the respective specialties, while the diseases share so much common underlying inflammation that they could be viewed as two expressions of the same disease (i.e., type2 disease). Moreover, for severe cases of both diagnoses, biologicals are widely employed but still only when at least one of the two reaches criteria for indication. A more general approach is an unmet need [30, 31]. To begin to close the gap between the two silos, an overarching questionnaire has been developed (the STARR-15) addressing CRS, and asthma, and allergic rhinitis, at the same time [32]. It still needs validation in the coming years but might serve as a promising tool for future collaboration and improved patient care.
Different co-morbidities have been suggested to go along with CRS, particularly in the primary diffuse type 2 patients. These manly included other type 2 disorders like bronchial asthma, eczema, allergies [33], eosinophilic esophagitis and NSAID intolerance [34] but also non-type 2 comorbidities like gastroesophageal reflux [35]. However, non-type 2 disorders are rarely the focus in CRS. A large Korean cohort study focused on autoimmune disorders and identified Sjögren's syndrome incidence to be associated with CRS with a hazard ratio (HR) of almost 1.7, mainly affecting chronic rhinosinusitis without nasal polyps (CRSsNP) patients. Other diseases including systemic lupus and ankylosing spondylitis where not associated [36]. It remains unclear, however, whether this is an association or the constellation of CRS with these non-type-2 comorbidities represents a specific form of secondary CRS .

The exact pathogenesis of CRS remains elusive [37]. Different mechanisms, however, have been identified to play key roles in the development of inflammatory subtypes and thereof resulting remodelling processes. In CRSwNP neo-osteogenesis is often found in severe and recalcitrant sub-forms and is associated with poorer prognosis [30, 31]. Lately, more light was shed on this specific topic in the context of extensive type 2 CRS. Elevated TGFbeta1 levels and alkaline phosphatase (ALP) protein were found in the bones of the sinuses of CRSwNP patients, which was positively correlated to in-vivo bone thickness. In these patients TGFbeta1 was co-localized with eosinophils and proved to promote bone mineralization in-vitro. Blocking TGFbeta1 in vitro lead to inhibition of ALP production as well as mineralization, which provides evidence for the roles of these two proteins in new bone formation and remodelling [38].

Developments in outcome measurements

Outcome measurements are central to our ability to judge the status of a patient's CRS as well as the efficacy of medical and surgical treatments [39-43]. Recent developments in our understanding of assessing outcomes for CRS have spanned across the entire breadth of outcome measurements. Outcome measures can be broadly classified as patient-reported outcome measu-

rements (PROMs), objective measures, psychophysical testing and biomarkers [44-46]. Recent, prominent advances that have expanded our understanding of these outcome measures, as well as how to use and interpret them in CRS have especially been made in relation to the assessment of CRS disease control and the role of objective outcome measurements.

Control of a disease can be defined as the extent to which the manifestations of that disease are within acceptable limits [47]. Control is a global measure of disease status and achievement of control serves as the goal of treatment for chronic disease [48, 49]. The first proposed definition of CRS disease control was in the 2012 European Position Paper on Rhinosinusitis and Nasal Polyps (EPOS) and was developed as expert opinion [50]. This definition is based on 7 criteria related to 5 symptoms (nasal obstruction, discharge, smell loss, facial pain/pressure and sleep disturbance), the need for systemic rescue medications (antibiotics or corticosteroids) for the patient's CRS, and the presence of nasal endoscopy findings, which together are used to classify a patient's CRS as controlled, partly controlled or uncontrolled [1, 50]. Although these criteria have conventionally been assessed in a dichotomous manner, more recent work has shown how visual analogue scale scores [51] or scoring on individual items of the 22-item Sinonasal Outcome Test (SNOT-22) may be used to assess the symptom criteria for this EPOS classification scheme [52]. Despite the significance of the EPOS definition and criteria for CRS control, studies have shown they often classify patients' CRS as less controlled than how both patients themselves and their healthcare providers would classify a patient's CRS control (53). In the last few years, research has been focused towards identification of criteria for CRS disease control that are derived in an evidence-based manner reflective of patients' and healthcare providers' perspectives, around which consensus could be built. For example, it has been shown through qualitative study including one-on-one interviews with CRS patients that these patients not only understand the concept of disease control but that patients' perspectives of CRS disease control align with those of providers as a global measure of their CRS that incorporates diverse manifestations and which serves as the goal of treatment [54, 55]. Moreover, as a reflection of patients' understanding and perspectives, a direct query of patients' self-assessment of CRS disease control has been validated as a measure of CRS disease burden [56]. Other studies have well characterized the primary determinants of both patients' and healthcare providers' assessments of a patient's CRS disease control [55, 57]. With a growing body of evidence as support, a recent international multidisciplinary panel of experts and patients identified consensus criteria for the assessment of CRS disease control [58]. This study identified overall symptom severity, patient-reported CRS control (i.e., a patient's assessment of their own CRS control), the severity of nasal obstruction and the need for CRS-related oral corticosteroids as consensus criteria for the assessment of CRS control, while "near-consensus" criteria were identified as the presence of nasal endoscopy, overall quality of life, impairment of day-to-day activities, the severity of smell loss, and the severity of nasal discharge [58]. These consensus and near-consensus criteria largely reflect the relative import and priority placed on each of these aspects of CRS by patients and healthcare providers [55-57, 59-61]. Moreover, debate around near-consensus criteria similarly mirrored the active discussions in the field today—especially as it relates to the role of nasal endoscopy findings.

Multiple staging systems have been developed to objectively quantify disease burden using nasal endoscopy and radiography (e.g., with CT scan) (12, 62-64). However, it has been demonstrated in multiple studies, including systematic reviews with meta-analysis, that objective outcome measures—which include nasal endoscopy findings or radiographic findings—correlate poorly with patient-reported outcome measures, for example their symptom severities or quality of life [15, 65, 66]. As a result, it has been asked whether treatment of nasal endoscopy findings (i.e., treating a patient specifically to improve nasal endoscopy findings) ultimately helps the patient [46]. While it has been argued that the presence of nasal endoscopy findings (for example, mucosal edema, discharge or nasal polyps) may represent a component of risk to the patient for clinical/symptomatic worsening, this has not yet been supported by evidence [58]. In the absence of evidence to drive how nasal endoscopy findings should be interpreted, a recent study investigated the practice patterns of experienced rhinologists from around the world, presenting different clinical scenarios of nasal endoscopy findings to them, and found that nasal endoscopy findings reflected by a total modified Lund-Kennedy (MLK) [64] score of ≥4 (out of 12) or total Nasal Polyp Score (NPS) [14] of ≥3 (out of 8) would lead to consideration for CRS treatment escalation, identifying these thresholds as possible indicators of lost endoscopic CRS control [67]. As a corollary, however, these results indicate that MLK score < 4 or NPS < 3 may indicate acceptable levels of nasal endoscopy findings in a CRS patient, reflecting endoscopic CRS control, and may serve as the goals of treatment rather aspiring to a complete absence of nasal endoscopy findings [67]. These findings represent a challenge to the existing paradigm for interpreting nasal endoscopy findings and possibly other objective outcomes by demonstrating that some level of positive findings may be acceptable.

Management developments

The management of Chronic rhinosinusitis (CRS) has changed significantly in the last decade. The most recent EPOS document proposed a new classification of CRS [1] based on three aspects: is it primary or secondary to another disease , is the disease localized or diffuse, and what is the presumed dominant endotype. This new classification significantly impacts CRS management. Localised disease is usually managed surgically

[68]. Diffuse disease, with generalized inflammation, needs anti-inflammatory treatment with surgery only in an adjunctive role. The possibilities of endo-typing the disease have led to further differentiation of treatment options and is now advised in guidelines like the EUFOREA pocket-guide [1, 11, 69]. Most CRS patients respond favourably to appropriate medical treatment such as nasal corticosteroids and saline nasal irrigation. If not, further treatment usually involves (F)ESS. A majority of the patients responds favourably to (F)ESS, with only 19% (95% confidence interval, 14 %-24%) of the patients needing revision surgery [70]. However, surgery and especially revision surgery can result in serious adverse events and outcomes are less favourable especially when olfaction is compromised [71, 72].

Until recently, patients with a type2-dominant endotype were frequently treated with courses of oral corticosteroids (OCS) in conjunction with nasal corticosteroids. OCS have a rapid and significant, but short-lived effect on the symptoms of type2 CRS, especially on olfaction. For that reason, historically, patients with severe uncontrolled disease were often treated with repetitive, or even with continuous low dose OCS, like in severe asthma. However, recent studies have further emphasized the detrimental (long term) effects of even limited amounts of OCS, like osteoporosis and diabetes mellitus [73]. Therefore, it is no longer warranted to treat with long term OCS in light of new treatment options.

A new development in CRS is the evaluation of treatable traits. Treatable traits are co-existing conditions and hence, therapeutic targets that can be identified by the patient's phenotypes and/or endotypes and are often overlooked in CRSwNP [17]. A typical treatable trait fulfils three criteria: identifiable/measurable, clinically relevant, and treatable [17]. Typical treatable traits that are often overlooked in the management of CRS are smoking [74], allergen exposure [28], co-morbidities [34, 75], occupation [76] and patient related factors [77, 78].

A breakthrough in the treatment of primary diffuse CRS has been the development of biologics for CRS with nasal polyps (in Western societies usually type2 CRS) [18, 79]. When considering treatment of CRS with biologics the otorhinolaryngologists has two things to consider: which patients are eligible for a biologic and what is the best biologic for this particular patient (80). In recent years, EPOS/EUFOREA have proposed a set of indication and evaluation criteria [1, 8, 18, 69, 81, 82]. The criteria involve type2 inflammation, impact on quality of life and smell, use of systemic corticosteroids and having asthma. It has been proposed to use biologics when at least three of these criteria are fulfilled on top of having had at least one ESS. Although it would be good to further evaluate the full extent and comprehensiveness of the ESS using the ACCESS score [83], there is no indication that biologics are not effective without surgery [40, 84]. The primary rationale for the recommendation for using biologics only after ESS is the effective nature of ESS [70] and the high cost of biologics [85]. In Europe, three biologics are approved by the European Medicines Agency: dupilumab [42, 43, 86, 87], mepolizumab [40, 41, 88] and omalizumab [89, 90]. In recent years a number of large series reporting on real world experiences have been published [87, 91, 92]. When considering a biologic for a patient, the second question is which biologic to choose. As far as we aware, there are no direct comparisons between the available biologics in the literature today. If the patient only has uncontrolled CRSwNP and the patient either has no asthma or the asthma is very well controlled, the (cluster meta)-analysis of the available evidence points to dupilumab as the most effective treatment [79, 93, 94]. When the patient also has severe asthma, warranting biological treatment, the considerations are more difficult, especially when considering different aims in asthma management, like exacerbation rates, asthma control, and FEV1 improvement [95]. A, from an otorhinolaryngologic perspective, very helpful paper from Pavord. et. al. proposes dupilumab in patients with severe asthma and CRSwNP when eosinophils are under 1500/ μl and/ or when the patient needs regular oral corticosteroids. When eosinophils are > 1500 they advise to investigate hyper-eosinophilic syndrome [96].

It is advised in the recent EPOS/EUFOREA to evaluate the efficacy/effectiveness of the biologic treatment after 6 months and 1 year [18]. If the disease remains uncontrolled either in the upper or lower airways switching to another biologics can be considered. Switching from an anti-IL5 treatment to dupilumab is usually succesful and it does not seem to be helpful to switch from one anti-Il5 treatment to another one [97, 98]. Moreover, biologic switching can be performed—and in many situations is advised to be done—without a washout period [97, 98].

Conclusion

The field of rhinology continues to advance at a rapid pace, improving our ability to understand and therefore treat out patients' diseases more effectively. Recent developments in the field in relation to pathophysiology, treatments and outcome measurements are already guiding the evolution our therapeutic approaches to rhinologic patients and it is hope that these developments—as well as continued their continued advancements—become widely accessible worldwide. Based on recent advances, we expect that treatment of rhinologic disease will become more precise, patient-dependent and pathophysiology-specific.

Abbreviations

ACCESS: Amsterdam Classification of Completeness of Endoscopic Sinus Surgery; ALP: alkaline phosphatase; AR: allergic rhinitis; BEC: blood eosinophil count; CRS: Chronic rhinosinusitis; CRSwNP: Chronic rhinosinusitis with nasal polyps; CRSsNP: Chronic rhinosinusitis without nasal polyps; eCRS: eosinophilic CRS; EPOS: European Positions paper on Rhinosinusitis and Nasal

Polyps; EUFOREA : European Forum for Research and Education in Allergy and Airway Diseases; (F)ESS: (Functional) Endoscopic Sinusi Surgery; FEV1: Forced expiratory volume in the first second; HPF: high power field; HR: hazard ratio; IL5: interleukin 5; MLK: Modified Lund-Kennedy; NAR: non-allergic rhinitis; N-ERD: NSAID exacerbated respiratory disease; NSAID: nonsteroidal anti-inflammatory drug; NPS: Nasal Polyp Score; OCS: oral corticosteroid; PROM: patient-reported outcome measurement; SNOT-22: 22-item Sinonasal Outcome Test; UK: United Kingdom.

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Conflict of interest

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