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Asthma and Chronic Rhinosinusitis with Nasal Polyps: Exploring Common Pathways and Treatment Approaches

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Abstract
Bronchial asthma (BA) is a chronic airway inflammatory disease characterized by the influx of cells, such as lymphocytes, eosinophils, and mast cells and, in a subgroup of patients, of neutrophils, in the bronchial wall [1,2]. The chronic inflammatory process leads to so-called airway remodeling [3]. Asthma is a variable condition in terms of clinical presentations (phenotypes) and distinct underpin pathophysiological mechanisms (endotypes). In fact, based on the biological mechanisms underlining the disease, asthma can be classified as a type 2 (eosinophilic) or non-type 2 (non-eosinophilic) endotype [4,5]. The endotypes referred to as "type 2 disease" are represented by an allergic variant either with or without eosinophilia and by the eosinophilic endotype without allergy [6,7]. In type 2 asthma endotypes, the biological mechanism involved in the inflammatory process is driven by T helper type 2 (Th2) cells, type 2 innate lymphoid cells (ILC2) and type 2 cytokines, including interleukin (IL)-4, IL-5, IL-9 and IL-13 [8]. Biomarkers, such as absolute eosinophil count in peripheral blood, total and specific IgE, and fractional exhaled nitric oxide (FeNO), may be used as indicators of type 2 asthma endotypes and help predict response to biologic therapies, now available for this variant

Keywords: bronchial asthma, nasal polyps, chronic rhinosinusitis, inflammation.

Introduction

Chronic rhinosinusitis (CRS) is a prevalent and heterogeneous disease associated with a high degree of morbidity. While there exist specific conditions for diagnosis, it has been increasingly appreciated that CRS exists as a spectrum of clinical conditions with distinct pathophysiology and presentation [1]. Targeted biologics for treating asthma are now being used for CRS with nasal polyps (CRSwNP), which has predicated the need for improved classification and diagnosis of different presentations of the disease in an effort to improve therapeutic efficacy.

Traditionally, a dichotomous classification system has been used to describe CRS based on the presence or absence of nasal polyps. CRS with nasal polyps (CRSwNP) represents a subset of those with CRS [2], and CRSwNP is often associated with more severe sinonasal symptoms and asthma. The division of CRS by polyp status was initially supported at the cellular level, with CRSsNP thought to be characterized by a

T_H1 predominant inflammatory pattern and CRSwNP characterized by a T_H2 predominant inflammatory pattern. However, recent work has demonstrated that CRS may be better evaluated as a continuum of inflammatory processes, with variable and non-mutually exclusive immunologic markers. This complexity can potentially be captured with endotype or cluster classification based on consistent pathological mechanisms that may not be evident at the level of phenotypic observation. Endotypes are often defined by the presence or absence of one or more biomarkers, and biomarker utilization can be helpful in achieving accurate diagnosis, evaluating optimal therapeutic strategy, and determining patient prognosis.

1) CRSwNP Pathophysiology

Inflammatory sinonasal polyps manifest bilaterally from the ethmoid sinuses, and can often present with hyposmia and/or nasal obstruction as major symptoms. It is thought that nasal polyp growth is present in 1–4% of the United States population [3]. As previously stated, TH2 inflammation often predominates, and is associated with elevated levels of eosinophils and Type 2 inflammatory cytokines including Interleukin (IL)-4, IL-5, and IL-13 [4]. Asthma is frequently a comorbid condition in CRSwNP patients, affecting 20–60% of diseased individuals [5]. An additional hallmark of CRSwNP is the loss of healthy barrier function in sinonasal epithelial cells. There is generally increased permeability, decreased epithelial resistance, and a high degree of tissue remodeling observed [6] in cells harvested from patients with CRSwNP, compared with cells from CRSsNP patients and control individuals. This loss of barrier function is reflective of a general inflammatory process, but it is unclear if the epithelial cells are inherently abnormal or if the state is induced [7]. Treatment for CRS is most frequently glucocorticoid-based, but response is quite variable in patients with nasal polyps, and side effects from oral steroids limits their long-term efficacy in the treatment of this disease. Hamilos et al demonstrated an inverse relationship between glucocorticoid receptor β expression in nasal polyp tissue and steroid efficacy, [8] while another study showed that neutrophil accumulation in nasal polyp tissue is also related to corticosteroid insensitivity [9]. Some individuals exhibit a very high level of resistance to steroid therapy, and this underscores the need for therapeutics targeted towards non-steroid-responsive pathophysiologic mechanisms involved in sinus polyp formation.

B. Pathogenic Mechanisms of Upper and Lower Airway Inflammation in Asthma and CRS

The immunopathogenesis of inflammatory processes behind BA and CRS has been clearly defined and, in the great majority of cases, is characterized by type 2 inflammation [27]. Type 2 inflammation is characterized by the presence of cellular infiltration as the result of a complex network of traditional mediators (prostaglandin-D2 (PGD2), leukotrienes, histamine, etc.), key type 2 cytokines (IL-4, IL-5, and IL-13), and chemokines (CCL-3, CCL-5, CCL-11) [2]. The production of type 2 cytokines

is sustained by several cellular actors, such as Th2 (both effector memory Th2 recruited from the blood and resident memory Th2 lymphocytes, ILC2, innate-like lymphocytes (ILL) as well as effector cells, namely represented by mast cells, basophils, and eosinophils [20]. Eosinophilic airway inflammation is the hallmark of disease severity in a subset of individuals with severe asthma, and a direct relationship between eosinophil count and the frequency of asthma exacerbations has been demonstrated [19]. It has been shown that, at least in allergic forms, IgE antibodies influence the functioning of several immune and structural cells of the bronchial wall. IgEs are primarily responsible non only for the acute phase but also for the chronic phase of inflammation characteristic of BA [14]. A role of IgE antibodies has also been proposed for CRSwNP [15].

Recently, much attention has been dedicated to IL-5- and IL-13-producing ILC2 significantly increased in sputum of patients with severe asthma with uncontrolled eosinophilia despite treatment with high-dose oral corticosteroids (OCS) [13]. Notably, also in CRS, an important source of type 2 cytokinesis represented by ILC2s. In fact, experimental data obtained in humans demonstrated that the number of ILC2s is increased in the nasal mucosa of patients with CRSwNP [3].

In asthmatic patients, the chronic inflammatory process at the bronchial level leads to airway remodeling where goblet cell hyperplasia, subepithelial collagen deposition, epithelial damage, airway smooth muscle hyperplasia and increased vascularity are the main features of the consequence of chronic stimulation by factors, such as leukotrienes and PGD2, or cytokines and chemokines as transforming growth factor (TGF)-β, IL-1, IL-6, CCL2, CCL3 [3]. Similar alterations have also been demonstrated in CRS. Indeed, in patients with CRSwNP, histopathological analyses have highlighted that, in addition to diffuse tissue eosinophilia and eosinophilic aggregates, basement membrane thickening, subepithelial edema and fibrosis are evident [14]. Therefore, upper and lower airway remodeling is the direct consequence of ongoing or cyclic inflammation and repair occurring in both asthma and CRS.

1) Cytokines

Cytokine profiles are perhaps the most currently investigated and initially promising biomarkers for CRS phenotyping and therapeutic targets. The classic characterization of CRSsNP is with a T_H1 or T_H17 phenotype with prominent neutrophilia, expressing Transforming Growth Factor β (TGF-β), type I interferons, and IL-6, IL-8, or IL-17. This is contrasted with the characterization of CRSwNP as a T_H2 microenvironment with increased expression of thymic stromal lymphoprotein (TSLP) and type 2 inflammatory cells, such as Type 2 Innate Lymphoid (ILC-2) cells, which produce IL-4, IL-5, IL-13, IL-25, and/or IL-33. ILC2 cells play a role in T and B cell activation, and activated epithelial cells contribute to leaky barriers as they apoptose [1]. Both IL-4 and IL-13 induce local IgE production and stimulate mucus secretion, while IL-5

induces eosinophilia through recruitment, activation, and survival of eosinophils [1]. IL-13 affects epithelial differentiation resulting in decreased ciliation and goblet cell metaplasia, further contributing to a leaky epithelial barrier of sinonasal epithelial cells [21]. IL-13 also increases hyper- reactivity of the airway and causes subepithelial fibrosis. More recently, studies show that IL-25 appears to be involved in the IL-13 regulatory cascade, with IL-25 stimulation inducing IL-13-dependent changes in an asthma mouse model [20].

Many anti-cytokine agents are currently in production and development as asthma treatments, and it is a logical extension that they may have a potential role in treating T_H2 inflammation in CRS. It has been well demonstrated that asthmatic patients with a T_H2 phenotype with eosinophilia derive benefit from IL-5 antagonists [2]. In fact, nasal polyps were a good biomarker for predicting anti-IL-5 response in these studies, due to the relationship of nasal polyps with a T_H2-skewed state. Antibodies to IL-5 already are approved for refractory asthma, and an anti-IL-5 receptor antibody will be available in a short time. Initial trials of IL-5 antagonism with mepolizumab and reslizumab in CRSwNP demonstrated a reduction in nasal polyp size and reduced necessity for revision surgeries [3]. However, these trials have not definitively shown improved nasal symptom scores, and careful patient selection may be critical for derivation of benefit. An IL-5-enriched endotype appears to be necessary to predict efficacy, as eosinophil markers themselves were not predictive of mepolizumab response magnitudes

2) Periostin

Periostin is an extracellular protein that is secreted in response to IL-4 and IL-13, and it plays a role in airway subepithelial fibrosis through interactions with integrin molecules involved in tissue remodeling [19]. Additionally, it participates in eosinophil recruitment and activation cascades as well as in angiogenesis through the action of vascular endothelial growth factor (VEGF) [10]. Periostin is elevated in CRSwNP patients regardless of asthma or atopic comorbidity status, and it is especially high in patients with active disease. Conversely, periostin levels appear to decrease following effective treatment and can be helpful in evaluating efficacy of therapy [21]. Specifically, an established cutoff value of 48.5 ng/ml of s-periostin had a sensitivity of 93.5% for the presence of tissue IL-5. Because periostin appears to regulate protein expression of other inflammatory molecules and tissue remodeling factors, there is potential for periostin itself to serve as a viable target for the reduction of inflammation [5]

3) Taste Receptors

Over the past several years, a growing body of literature has identified a role for bitter and sweet taste receptors in immune defense in the airway [5, 6]. Bitter taste receptors respond to bacterial products, including acyl-homoserine lactones produced by gram-negative bacteria such as Pseudomonas aeruginosa [17]. When bitter taste receptors on

ciliated cells are stimulated, there is a downstream antimicrobial nitric oxide response, resulting in direct bacterial killing and increases in ciliary beat frequency [18]. When a separate cohort of bitter taste receptors on solitary chemosensory cells, another airway cell type, are stimulated, antimicrobial peptides are released [19]. Bitter taste receptors are genetically diverse, and specific genetic polymorphisms correlate with in vitro antimicrobial activity of sinonasal epithelium [16]. This translates to the clinical realm; patients with a non-functional polymorphism in a specific taste receptor, T2R38, have inferior outcomes following functional endoscopic sinus surgery and require increased intervention [22]. Furthermore, sinonasal specimens from patients with non-functional polymorphisms exhibit increased bacterial biofilm formation [11]. Some in vitro studies also show that bitter taste receptor hyper-activation can be deleterious and potentially pro-inflammatory, as sinonasal cultures obtained from patients with CRSwNP have increased disease recurrence following sinonasal surgery.

4) Microbiome

The nasal microbiome is thought to play an important role in CRS pathogenesis, and several studies have shown that bacterial diversity is decreased in disease while overall bacterial abundance is increased [14]. This suggests that dysbiosis is correlated with CRS status [2]. Beyond this, Cope et al demonstrated specific microbiota classifications that correlated with patient phenotypes, including the presence of nasal polyps [7]. A higher than expected proportion of patients with CRSwNP are colonized with Staphylococcus aureus [8], and IgE antibodies to S. aureus enterotoxins are frequently found in diseased tissue specimens. Both S. aureus and P. aeruginosa bacteria can disrupt the epithelial barrier contributing to presumed physiologic mechanisms for CRSwNP development. Compounding the problem, antimicrobial compounds including lysozyme, S100 proteins, and β-defensins all are decreased in CRSwNP patients compared to matched controls [9]. This reduction in natural defenses could play a key role in shifting the balance towards dysbiosis. Finally, an alternative proposed pathogenic mechanism for T_H2-biased sinusitis is that T-cells are allergically sensitized to fungi in the ambient environment, leading to allergic inflammation characterized by a T_H2-high state [4].

C. Clinical Efficacy of Biological Agents in Asthma and CRS

As previously mentioned, blocking free IgE omalizumab interrupts the IgE-mediated asthma inflammatory cascade at an early stage, thus reducing both early and late asthmatic responses, and improving lung function, asthma control and decreasing the number of exacerbations. A greater effect of exacerbation reduction was observed in patients with high FeNO and periostin levels and high peripheral blood eosinophil counts [8,9]. The clinical use of omalizumab has been recently extended to the treatment of patients with refractory CRSwNP. In fact, in addition to preliminary data of a proof-of-concept study and real-life experience, two phases 3 studies with omalizumab [21] demonstrated the improvement of −1.08 and −0.89 in nasal polyp

score (NPS) and mean daily nasal congestion score (NCS), respectively, with better outcomes and patient-reported assessments of symptom severity. The treatment was also able to improve sinonasal outcome test (SNOT)-22 and overall impact on patients' quality of life (QoL) [3].

The last approved mAb, dupilumab, has been demonstrated to significantly reduce the rates of severe asthma exacerbations and OCS use by improving lung function. The greatest treatment benefits have been observed in patients with high peripheral blood eosinophils counts and FeNO levels [8,9]. Of note, dupilumab has been the first biological agent approved for the treatment of CRSwNP. In fact, in adult patients with severe CRSwNP enrolled in the two trials [2], dupilumab reduced polyp size, radiological sinus opacification, and symptom severity. The major mean difference in NPS under dupilumab treatment versus placebo was –2.06, whereas the difference in nasal congestion was −0.89 [21]. More important, in the first study, dupilumab also improved the Lund-Mackay computer tomography scores (−7.44) [20].

D. Asthma and CRS May Display Different Clinical Outcomes in Response to Biological Treatment

In addition to demonstrating the efficacy of biological agents targeting type 2 inflammation, asthma clinical trials and real-life studies have highlighted a range of responses to treatment [5,6]. The existence of a range of responses is evident when considering the OCS-sparing effect. In fact, a proportion of patients reach complete OCS intake interruption, while others only reduce OCS dose or need to maintain the original OCS dose used before biological treatment. A similar consideration can be made if we analyze the variability of the clinical outcomes in treated subjects. In fact, while some patients experienced exacerbations, some even severe, others remained exacerbation-free throughout treatment. Asthma and nasal symptom responses may also vary between biologicals due to differences in target, dosing, administration interval and patient baseline characteristics, such as body mass index (BMI) and comorbidities. It has been demonstrated that anti-IL-5/IL-5Rα strategies and omalizumab are more likely to be effective in patients with high blood eosinophil count and in those with OCS maintenance dose therapy. Similar data have been observed for dupilumab also concerning baseline FeNO levels and OCS dose [2,22]. It should be underlined that clinical response may vary over the course of treatment differently between asthma and CRS control.

Many questions regarding responders and nonresponders, predictors of response, and residual disease after blocking type 2 pathways are still unanswered. For example, asthma and CRS can coexist but with different degrees of severity; therefore, efficacy may not be equally achieved. In clinical practice, it is common to experience that patients reach a good clinical response for asthma symptoms, but not for CRS, as reported in some small case series [15]. Moreover, in individual patients, biological mechanisms underpinning asthma and CRS can be only partially similar, not only in

terms of severity but also in terms of cellular and molecular "actors" driving the inflammatory process. As mentioned above, the accumulation of eosinophils is a type 2 disease hallmark but not always responsible for the full-blown inflammatory process, including remodeling in different compartments. Directly or indirectly targeting eosinophils can result in partial and/or varying improvement of clinical symptoms [16]. The administered biological dose may represent another potential factor influencing the clinical effects due to a variable capacity of reaching a higher concentration at the tissue level. Indeed, in the clinical trial using 750 mg of mepolizumab intravenously, the need for polyp surgery was significantly reduced, and a significant reduction of endoscopic NPS was observed [7,8]. This hypothesis is supported by Mukherjee et al. [9], who demonstrated an improved response to the weight-based anti-IL-5 mAb reslizumab in patients who still had sputum eosinophilia despite mepolizumab treatment. On the other hand, in a high proportion of EGPA patients treated with mepolizumab 100 mg subcutaneously (sc), a clinically important difference in SNOT22 was observed even though the approved dose in such patients is 300 mg sc [10].

Individual differences in pharmacokinetics and resulting plasma drug levels are additional interfering factors, as demonstrated in other chronic immunomediated diseases in which mAbs are largely used. The pharmacokinetics of mAbs is characterized by low extracellular compartment distribution due to their large molecular size and long elimination half-life . The rate and extent of absorption vary between mAbs and between individuals for the same mAb. This raises the possibility that, in some patients with a high BMI, the standard dose may be insufficient to reduce airway and nasal inflammation in the same manner.

Conclusions

In the last few years, the role of the pathogenic mechanisms active in BA and CRS has been further defined, improving the knowledge of potential therapeutic targets. Taking into account the significant proportion of patients in which the two diseases coexist, and the common underpinned cellular and molecular inflammatory network, at least in type 2 forms, it was believed that by using the available biological agents, we could obtain an equivalent therapeutic effect for both asthma and CRS. Although this is true in several patients, in a non-negligible number of them, the improvement of nasal symptoms is less evident, despite reaching satisfactory asthma control. Many questions still need to be answered, specifically referring to the different tissue inflammatory consequences, such as remodeling at the bronchial and nasal levels; the different intensity of the inflammatory process or the existence of two different patterns of inflammation at the bronchial and nasal levels (type 2 and non-type 2 variants); the ability of biological agents to equally reach the different tissue sites. Future studies

focusing on tissue samples from the upper and lower airways in response to biological treatment could allow defining the relationship between these two compartments.

1) Key Points:

- Chronic rhinosinusitis is a complex disease that exists along the inflammatory spectrum between type 1 and type 2 inflammation.
- The classic phenotypic differentiation of CRS based on the presence or absence of inflammatory polyps, to-date, remains one of the best differentiators of response to medical and/or surgical therapy.
- The advent of biologics in the treatment of atopic disease and asthma, and perhaps a new look at topical therapies for sinusitis has placed renewed emphasis on understanding the pathophysiology of inflammatory sinus polyp pathogenesis.
- Identification of key markers of polyposis will allow for better stratification of inflammatory polyp disease endotypes to objectively identify tailored medical therapies and track response to medical and surgical treatment.

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