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Current and future treatment options for adult chronic rhinosinusitis: Focus on nasal polyposis

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Activity Objectives:

1. To understand the phenotypes and endotypes of chronic rhinosinusitis (CRS).
2. To review the concept of T_H2-biased inflammation in patients with chronic rhinosinusitis with nasal polyps (CRSwNP).
3. To appreciate the clinical features of this inflammatory endotype.
4. To review targets of intervention for T_H2-biased disease.

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Chronic rhinosinusitis (CRS) affects more than 10% of the population in the United States and Europe. Recent findings point to a considerable variation of inflammatory subtypes in patients with CRS with nasal polyps and patients with CRS without nasal polyps. According to current guidelines, glucocorticosteroids and antibiotics are the principle pharmacotherapeutic approaches; however, they fail in a group of patients who share common clinical and laboratory markers. Several clinical phenotypes often leading to uncontrolled disease, including adult nasal polyposis, aspirin-exacerbated respiratory disease, and allergic fungal rhinosinusitis, are characterized by a common endotype: a T_H2 bias is associated with a higher likelihood of comorbid asthma and recurrence after surgical treatment. As a consequence, several innovative approaches targeting the T_H2 bias with humanized mAbs have been subjected to proof-of-concept studies in patients with CRS with nasal polyps with or without comorbid asthma: omalizumab, reslizumab, mepolizumab, and recently dupilumab. Future concepts using upstream targets, such as GATA-3, also focus on this endotype. This current development might result in advantages in the treatment of patients with the most severe CRS. (J Allergy Clin Immunol 2015;136:1431-40.)

Key words: *Chronic rhinosinusitis, nasal polyps, T_H2, IL-5, IL-4, IL-13, GATA-3, IgE, humanized and fully human mAbs, gene silencing*

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Chronic rhinosinusitis (CRS) is now recognized as a disease affecting about 10% of the adult population in industrialized countries. Clinicians differentiate phenotypes of the disease on the basis of clinical signs; however, recent efforts help to recognize endotypes based on specific pathobiological mechanisms. It appears that both disease recurrence after pharmacotherapy and surgery and also lower airway comorbidity are associated with a significant T_H2 bias; this knowledge helps to guide future disease management approaches. Thus where the

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Abbreviations used
AERD: Aspirin-exacerbated respiratory disease
AFRS: Allergic fungal rhinosinusitis
CRS: Chronic rhinosinusitis
CRSsNP: Chronic rhinosinusitis without nasal polyps
CRSwNP: Chronic rhinosinusitis with nasal polyps
CT: Computed tomography
ESS: Endoscopic sinus surgery
GCS: Glucocorticosteroid
hmAb: Humanized mAb

current guidelines on available treatment options in patients with CRS end, a new area of interest has developed over the last years. Within a short time period, humanized mAbs (hmAbs) will be available for the treatment of severe CRS, specifically chronic rhinosinusitis with nasal polyps (CRSwNP). This review intends to describe the unmet needs of today and the possible answers of the near future.

EPIDEMIOLOGY AND BURDEN OF DISEASE

Recent epidemiologic studies have revealed wide variations in the prevalence of CRS among regions globally (Fig 1). The National Health Interview Survey of 34,525 US citizens showed that 12% of the adult population have been told by health professionals that they have sinusitis.[1] In Europe a postal questionnaire survey of 57,128 subjects from 12 countries reported the overall prevalence of CRS to be 11%, with marked geographic variations from 7% to 27%[2] by using the European Guidelines on Sinusitis and Nasal Polyposis criteria[3]; the appropriateness of such criteria for epidemiologic purposes has been confirmed.[4] Heath Surveys from Korea,[5] China,[6] and Brazil[7] revealed prevalences for CRS from 5.5% to 8%, with regions in China reaching 10% of the population. A consistent and exposure-related association of CRS with smoking has been observed in Europe[2] and confirmed in China.[6] The prevalence of CRS was higher in female than in male subjects among US and European citizens,[1,2] whereas the situation was the opposite in China.[6]

By using the 36-item Short-Form survey, CRS has been demonstrated to negatively affect several aspects of quality of life and has a greater effect on social functioning than chronic heart failure, chronic obstructive pulmonary disease, or back pain.[8] The validated Sino-Nasal Outcome Test reported a median value of 7 in healthy volunteers compared with a mean preoperative score of 42 in a cohort of 3128 patients undergoing surgery for CRS.[9] Pain is a prominent quality of life–decreasing factor in patients with chronic rhinosinusitis without nasal polyps (CRSsNP), whereas nasal obstruction and comorbid asthma have a major effect in patients with CRSwNP. The total cost for treating 1 patient with CRS was estimated to be $2600/y in the United States; CRS is one of the top 10 most costly health conditions to US employers, with direct annual costs of $8 billion US dollars.[10] In Europe the direct cost of a patient treated in a university hospital for severe CRS was $1861/y.[3] Patients with recurrent CRSwNP produce the highest costs; 57% of nearly 400 patients with CRSwNP/allergic fungal rhinosinusitis (AFRS) reported having undergone previous endoscopic surgery, of which 46% reported having undergone more than 1 operation in a recent United Kingdom audit.[11]

FROM PHENOTYPES TO ENDOTYPES

Current consensus in Europe and the United States discerns 2 major phenotypes defined as subgroups of patients with homogeneous clinically observable characteristics[3,12] based on nasal endoscopic and computed tomographic (CT) findings: CRSwNP and CRSsNP. Furthermore, there are additional subtypes based on underlying conditions, such as AFRS, CRS associated with aspirin-exacerbated respiratory disease (AERD), CRS in patients with cystic fibrosis, primary ciliary dyskinesia, systemic diseases, or immune deficiency; these can present as CRSwNP or CRSsNP. Additionally, subjects might have comorbidities, such as inhalant allergies and asthma.

Current therapy approaches are oriented on these phenotypes and described in US and European guidelines or practice parameters.[3,12] For future treatment approaches, however, which will likely make use of hmAbs, the central pathophysiologic mechanism that induces and maintains the disease is of great importance.[13] These pathomechanisms represent the targets for intervention, and because a disease phenotype can have various pathomechanisms, there might be several targets for one phenotype. At this level, clinically defined phenotypes are not sufficient to develop indications for treatment; we need to base new approaches on endotypes of CRS, which are defined as "subtypes of disease with a unique pathomechanism, functionally and pathologically different from others by the involvement of a specific molecule or cell."[14] Endotypes could be differentiated on the cells involved, such as the abundance of eosinophils or neutrophils, on T helper cell populations or levels of IgE or cytokines, including IL-4, IL-5, or IL-13.

In general, eosinophilic CRS is associated with steroid responsiveness, whereas neutrophilic polyps are less sensitive to glucocorticosteroids (GCSs).[15] Furthermore, mucosal eosinophilia can be used to predict nasal polyp recurrence. Mucosal eosinophilia exhibits significant geographic and ethnic differences; pronounced eosinophilic infiltration is predominant in Western white patients with CRSwNP,[16] whereas the eosinophilic phenotype constitutes less than half of the CRSwNP cases in East Asia.[17]

To date, a study by Nakayama and colleagues[18] has identified 4 subgroups of CRS based on eosinophilic inflammation patterns and clinical presentation in Asian patients. Recently, Lou et al[19] used unsupervised hierarchical cluster analysis to generate 5 clusters based on the presence of predominantly plasma cells, lymphocytes, neutrophils, eosinophils, or mixed inflammatory cells in a large cohort of patients with CRSwNP and showed that these clusters would be associated with differences in polyp recurrence.

With the availability of various hmAbs to specifically target cytokines and their receptors, the role of key cytokines in disease subtypes reaches the utmost importance. Studies have demonstrated that T_H2-biased cytokine profiles, with IL-4, IL-5, and IL-13 as prominent cytokines, are key features of eosinophilic CRSwNP,[20] comprising the majority of patients in Europe and the United States, whereas neutrophilic CRS has been shown to be characterized by a significant increase in T_H1/T_H17 cell patterns, predominating in Asian patients[21]; these would express increased protein levels of IFN-γ, IL-17, or both. However, there is evidence for a different distribution of such patterns among patients with CRS and of different concentrations of cytokine proteins detected in tissue of Asian and European patients, but the individual