

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

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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

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 criteria³; the appropriateness of such criteria for epidemiologic purposes has been confirmed.⁴ Heath Surveys from Korea,⁵ China,⁶ and Brazil⁷ 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 Europe² 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 colleagues¹⁸ has identified 4 subgroups of CRS based on eosinophilic inflammation patterns and clinical presentation in Asian patients. Recently, Lou et al¹⁹ 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 patients²¹; 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

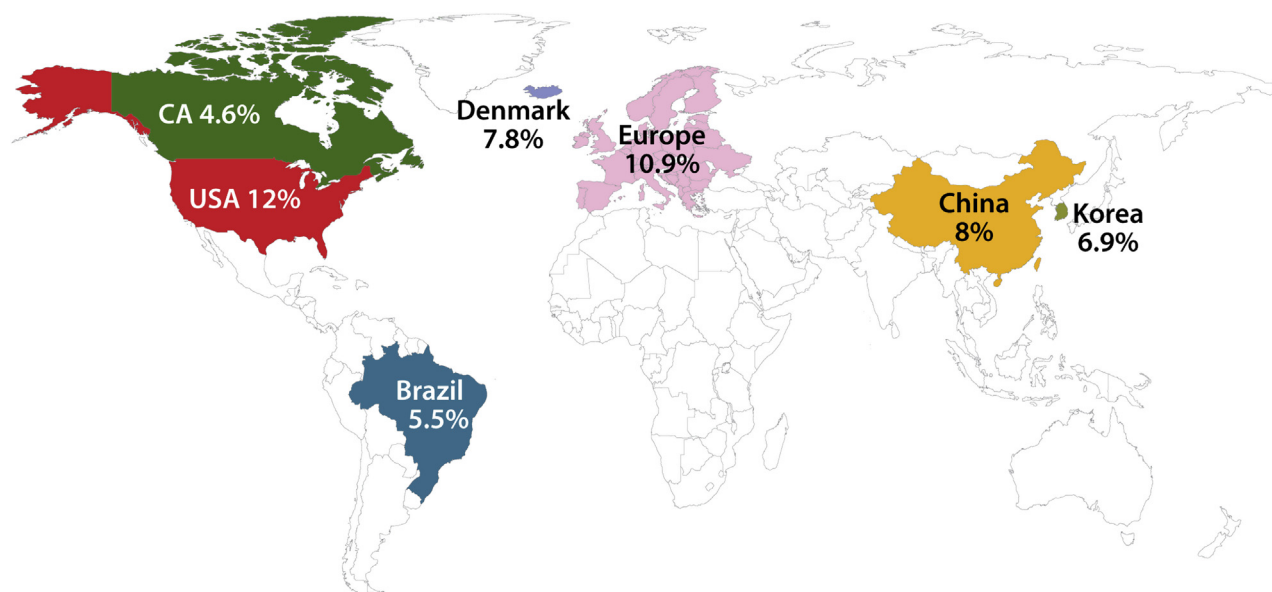


FIG 1. Prevalence of CRS in different regions of the world.

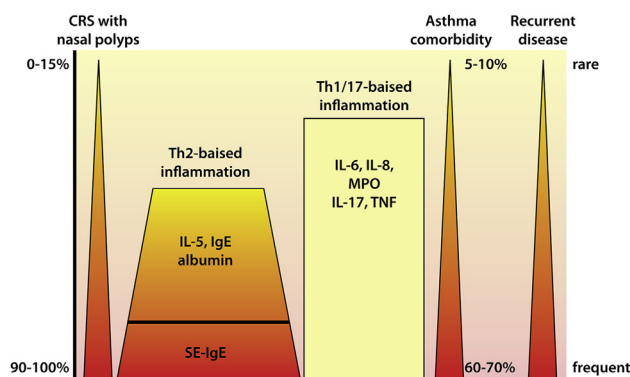


FIG 2. Inflammatory subtypes and associations with presence of nasal polyps, asthma, and recurrence. This graph is based on an analysis defining clusters based on cytokine expression, IgE levels, and mediators (P. Tomassen, et al, 2015). T_H 2-biased inflammation is associated with the presence of polyps, asthma comorbidity, and the likelihood of recurrence. MPO, Myeloperoxidase; SE-IgE, IgE to staphylococcal enterotoxins.

cytokine patterns are very consistent worldwide (X. D. Wang, personal communication). In a recent study using biomarkers in an unsupervised cluster analysis approach, 6 of 10 clusters were characterized by expression of moderate or high concentrations of IL-5, eosinophil cationic protein, and IgE (P. Tomassen, et al, in review). Two of the clusters expressed IgE antibodies to *Staphylococcus aureus* enterotoxins; these were associated with mucosal presence of *S aureus* and the highest concentrations of IgE, eosinophil cationic protein, and IL-5 but also comorbid asthma and recurrence (Fig 2). Patients with CRSsNP expressing high concentrations of TNF- α and IL-22 in tissue were associated with the mucosal presence of *Pseudomonas aeruginosa*.²²

ASTHMA COMORBIDITY, ASPIRIN HYPERSENSITIVITY, AND DISEASE RECURRENCE AFTER SURGERY

The link between CRS and asthma has long been documented and correlated to sinus CT scores and eosinophils in peripheral

blood and induced sputum.^{3,12} Especially patients with CRSwNP are prone to severe asthma. Studies involving large series of patients with CRSwNP show an incidence of asthma between 20% and 70%.^{23,24} About 7% of asthmatic patients have CRSwNP, with a higher incidence in patients with nonatopic asthma (13%).²³ Evidence is accumulating that the lower airways have the same inflammatory profile as the upper airways. Even more, the presence of high levels of IL-5 and specific IgE against *S aureus* in nasal polyp tissue predicts comorbid asthma.²⁴

A subset of patients with CRSwNP have Samter triad, now termed AERD, which is characterized by hypersensitivity to aspirin and nonsteroidal anti-inflammatory drugs, CRSwNP, and asthma. About 15% of patients with polyps have aspirin sensitivity.^{3,12} Zhang et al²⁵ found that IgE antibodies to staphylococcal enterotoxins can be found in tissue of the majority of patients with CRSwNP who are aspirin sensitive. The unusual severity of upper airway disease in these patients is reflected by high recurrence of nasal polyps and frequent need for sinus surgery.

Recently, we demonstrated that about 80% of patients with CRSwNP had recurrence and about 37% needed revision surgery in a prospective follow-up study over 12 years after initial surgery.²⁶ The need for revision surgery was higher in patients with increased eosinophil counts and IL-5 and IgE levels in nasal tissue measured in baseline biopsy specimens.²⁷ Furthermore, the presence of respiratory allergy was also associated with higher recurrence and revision rates. Although as frequent in patients with CRSwNP as in the general population, allergy, which is known to be associated with a T_H 2 bias, also predicted recurrence.

CURRENT TREATMENT RECOMMENDATIONS AND UNMET NEEDS

The primary goal of the treatment is to achieve and maintain clinical control. Control is defined by the European Guidelines on Sinusitis and Nasal Polyposis 2012 as a disease state in which patients do not have bothersome symptoms combined with a

TABLE I. Reported studies with hmAbs in nasal polyposis

Antagonist	Target	Year	Therapeutic effects	Limitations	Status of development
Omalizumab ³⁹	IgE	2013	Significant reduction of polyp and CT scores, improvement of symptoms of upper and lower airways and quality of life	No reduction of serum or nasal secretion mediators, frequent rhinopharyngitis	PoC
Mepolizumab ⁴⁰	IL-5	2011	Significant reduction of polyp score, reduction of blood eosinophil count, as well as ECP and IL-5R α levels, in serum	No significant improvement of symptoms, frequent rhinopharyngitis	Clinical trial, phase 3
Reslizumab ⁴¹	IL-5	2006	Significant reduction of polyp score, reduction of blood eosinophil counts, as well as ECP levels, in serum	No significant improvement of symptoms	PoC
Dupilumab ⁴²	IL-4R α	2015	Significant reduction of polyp and CT scores, improvement of smelling, symptoms, and quality of life (SNOT-22); improvement of pulmonary function (FEV ₁) and asthma control test score (ACQ5)	Side effects include headache, rhinopharyngitis, and reaction at injection site	PoC

ACQ5, Five-item Asthma Control Questionnaire; ECP, eosinophil cationic protein; IL-4R α , IL-4 receptor α ; IL-5R α , IL-5 receptor α ; PoC, proof of concept; SNOT-22, Sino-Nasal Outcome Test.

healthy or almost healthy mucosa and the need for local medication only.³

Treatment of CRSsNP

Topical GCSs have demonstrated beneficial effects on symptoms in patients with CRSsNP compared with placebo.^{3,12} Long-term topical GCS treatment is well tolerated, and adverse events are minor; topical GCSs are part of standard treatment.

Oral corticosteroids are occasionally administered in conjunction with antibiotics or topical GCSs, although there is a lack of evidence showing efficacy as monotherapy,²⁸ and side effects must be considered.^{29,30}

Short-term broad-spectrum antibiotic treatment in patients with CRSsNP is only relevant to treat acute exacerbations.^{3,12} Long-term macrolide treatment can have additional anti-inflammatory effects; 2 randomized controlled trials show conflicting results.^{31,32} Wallwork et al³¹ suggest that macrolides might have a beneficial role in the treatment of CRS with low serum IgE levels, but rationale and prospective studies to support this claim are lacking.³¹

Saline solutions are frequently used as supplements to other therapies and in various forms. They reduce symptoms as monotherapy and are supported by meta-analyses and guidelines.^{3,12}

The aim of surgery is to restore sinus ventilation and drainage by opening the key areas and preserving the sinus mucosa. Today, endoscopic sinus surgery (ESS) is the standard procedure for chronic sinus disease and associated with decreased morbidity compared with previous more invasive procedures.³ More evidence for the efficacy of ESS in patients with CRSsNP and the appropriate time point of intervention, as well as follow-up pharmacotherapy, is needed. ESS is associated with improvements in nasal symptoms and quality of life.³³ The need for revision surgery in patients with CRSsNP is estimated to be around 10%.³⁴

Treatment of CRSwNP

Topical GCSs demonstrated significant benefit when compared with placebo on nasal symptoms, nasal polyp size, and nasal airflow.^{3,12} Nasal drops are likely to be more effective than sprays because of their distribution within the sinus cavities, specifically postoperatively.³⁵ Local side effects are epistaxis and nasal

irritation, and patients need to be advised about the correct delivery technique; systemic side effects are negligible.

Oral GCS treatment demonstrated effects on nasal polyp size, nasal symptoms, and nasal expiratory peak flow with a maximal effect after 2 weeks, but the treatment effects are short lived.³⁶ The chance of significant side effects increases with the dose and duration of treatment, and therefore long-term high-dose treatment is discouraged.^{3,12} In a retrospective study in 86,368 subjects, annual depot steroid treatment was associated strongly with an increased risk of diabetes and osteoporosis.²⁹ Furthermore, in patients with severe CRSwNP and several oral GCS bursts per year, 43% had osteoporosis and 49% had secondary adrenal insufficiency.³⁰ The use of short courses of systemic GCSs or depot steroid injections should be abandoned as a long-term treatment strategy and therefore are not part of the standard treatment schemes for CRSwNP.

One randomized controlled trial showed that 100 mg of doxycycline for 3 weeks had a moderate but long-term effect on nasal polyp size and postnasal discharge compared with placebo.³⁶ In practice, we use this approach in combination with topical GCSs.

There is no consistent evidence for leukotriene antagonists as monotherapy or add-on therapy.³ Oral aspirin desensitization has been investigated in several case series of patients with AERD, without showing a consistent clinical benefit.^{37,38} Therefore it is currently only recommended for clinical trials.

Sinus surgery should be considered in patients whose symptoms do not improve after maximal medical treatment. It results in reduction of nasal symptoms and improvement of quality of life.³⁹ Reduction in polyp size is more extensive compared with that after medical treatment. However, in a specific inflammatory endotype, recurrence of disease over 5 to 10 years is frequent despite parallel anti-inflammatory treatment.

Thus despite all possible and acceptable therapeutic measures, there is a subgroup of patients characterized by recurrent disease and asthma comorbidity with T_H2-type inflammation who require further innovative treatment approaches (Table I).³⁹⁻⁴²

ANTI-IgE hmAbs

Omalizumab is an hmAb binding to free IgE with high affinity, which is approved in the European Union and United States for the treatment of severe allergic asthma. Given the high mucosal

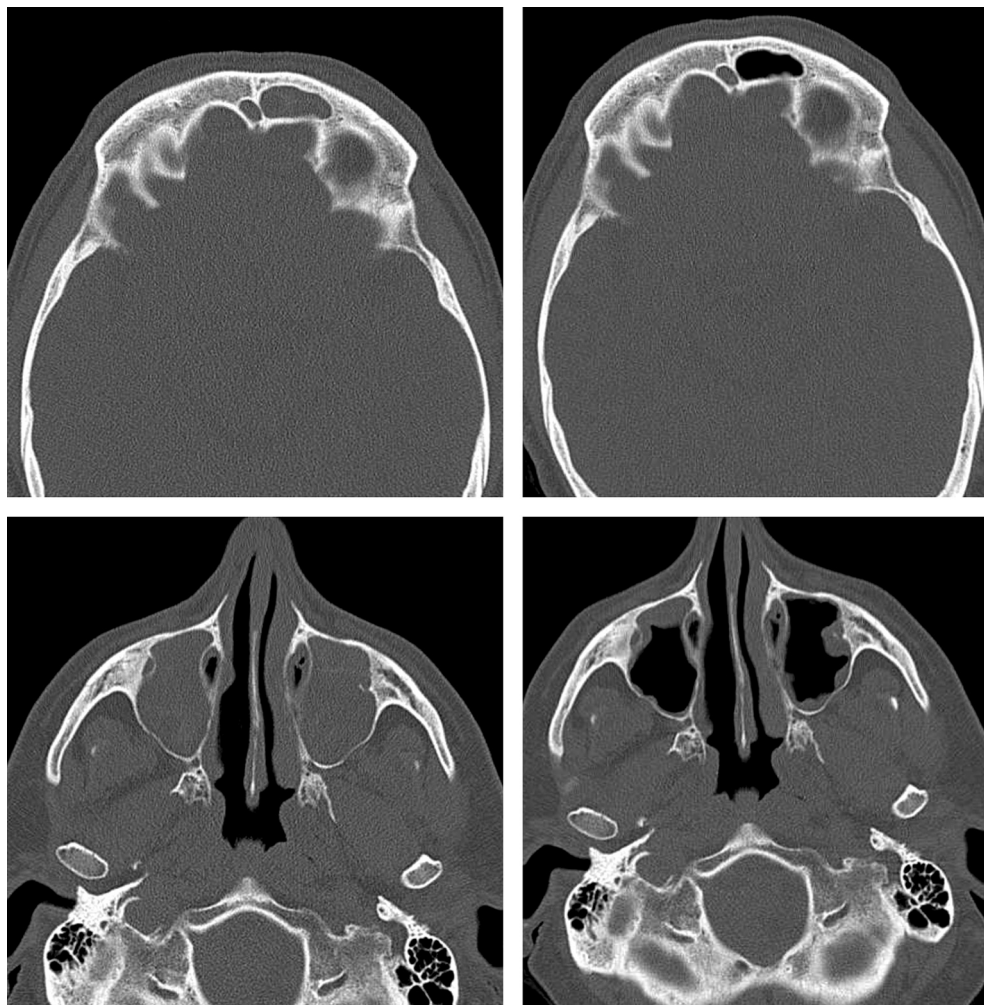


FIG 3. CT scans of the sinuses before and 3 months after omalizumab therapy.

IgE concentrations in nasal polyp tissue and their relevance for disease severity and comorbidity, strategies to antagonize IgE might be relevant in patients with CRSwNP. In a randomized, double-blind, placebo-controlled study of allergic and nonallergic patients with CRSwNP and comorbid asthma ($n = 24$), omalizumab significantly decreased total nasal polyp scores and sinus opacification (based on CT scan evaluation, Fig 3) and improved nasal symptoms, including sense of smell, in allergic and nonallergic subjects.⁴³ Additionally, omalizumab significantly improved asthma symptoms and quality of life (Asthma Quality of Life Questionnaire) irrespective of the presence of allergy. Recent observations demonstrating efficacy in patients with nonallergic asthma support these findings.⁴⁴

The results of another trial with omalizumab were negative, possibly because of the inclusion of patients with CRSsNP.⁴⁵ This underlines the importance of patient selection; those subjects with increased tissue IgE concentrations might be more likely to respond to the treatment, and comorbid asthma is a marker for high tissue IgE levels.²⁴ Observations in patients with severe asthma and CRSwNP receiving omalizumab in clinical practice support this notion because both the upper and lower airways reacted favorably to the treatment (I. Sintobin, personal communication).

Because of the late stage in the development of omalizumab, large randomized controlled trials will not be performed with omalizumab for the indication of CRSwNP; however, several case and small series reports point to the use of hmAbs in daily practice already outside of the indication.

QGE031, ligelizumab, a novel high-affinity anti-IgE antibody with greater affinity for IgE compared with omalizumab, was recently tested in 2 safety studies in atopic patients.⁴⁶ The greater affinity for IgE could possibly translate into a better suppression of free IgE and superior pharmacodynamic effects. Therefore QGE031 might benefit patients unable to receive or suboptimally treated with omalizumab because of high serum IgE concentrations.

ANTI-IL-5 hmAbs

About 80% to 85% of patients with nasal polyps in the United States and Europe demonstrate a T_H2 -biased inflammatory pattern with prominent eosinophilia and tissue expression of IL-5 protein and chemokines, as well as activation markers for eosinophilic granulocytes. Because IL-5 plays a key role in chemotaxis, differentiation, activation, and survival of eosinophils and because those cells represent such a prominent

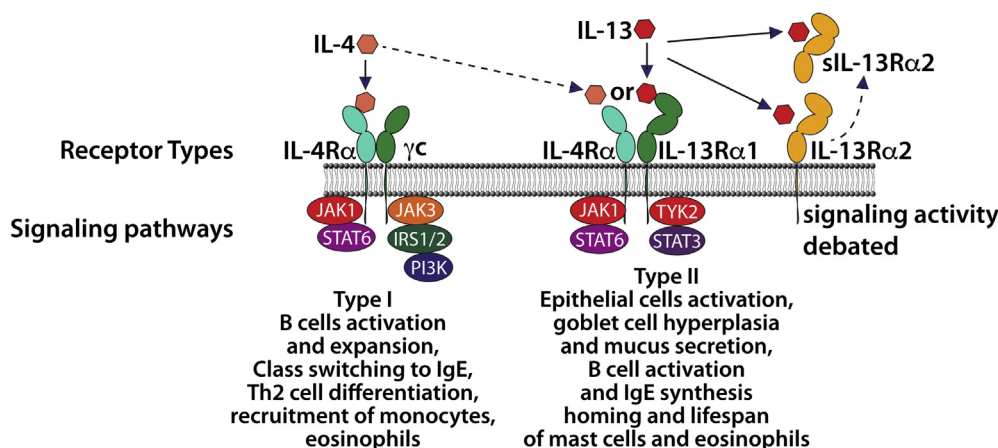


FIG 4. Principles of dupilumab therapy. By binding to IL-4 receptor α (IL-4R α), pathways for IL-4 and IL-13 are blocked. IL-13R α , IL-13 receptor α ; IRS1/2, insulin receptor substrate 1/2; JAK, Janus kinase; PI3K, phosphoinositide 3-kinase; STAT, signal transducer and activator of transcription.

characteristic in the polyps, antagonism of IL-5 was considered a therapeutic target. However, it was unclear whether anti-IL-5 hmAbs would reach the polyps and lead to a reduction in eosinophil counts with consecutive shrinkage of nasal polyps because polyp formation is possible without eosinophilia and the association of eosinophils with tissue edema was unclear.

In 1997, IL-5 was identified as a key cytokine in nasal polyposis⁴⁷; among a series of cytokines, IL-5 was strongly associated with eosinophilia and could be demonstrated immunohistochemically in eosinophils so that the cells themselves could be identified as a source of the cytokine. In the same year we could also show in an *ex vitro* polyp tissue model that anti-IL-5 antibodies, but not anti-IL-3 or anti-GM-CSF antibodies, induced eosinophil cell death (apoptosis).⁴¹ Later, it was revealed that regulation of IL-5 receptors plays a significant role in localization of the cells in peripheral tissues.⁴⁰ A first pilot study with reslizumab, a humanized anti-IL-5 antibody, showed a significant reduction of the size of the polyps in half of 24 nonselected patients after a single intravenous injection. A high IL-5 level in nasal secretions seemed to predict the therapeutic response and was suitable to monitor the response to treatment.⁴⁸ Hence the principle of IL-5 antagonism was established in eosinophilic nasal polyps.

In a study applying 2 intravenous injections of 750 mg of mepolizumab in 30 patients with severe nasal polyposis (polyp score of 3-4 or recurrence after surgery) refractory to topical GCSs, the therapeutic results were largely confirmed.⁴² After 16 weeks, a significant reduction of the polyp score of at least 1 point was found in 60% of the patients treated with mepolizumab in parallel to a significant reduction of CT scores (-4.0 vs $+0.5$ [placebo]). In the verum group the polyp score significantly decreased by 2.6 points compared with scores in those receiving placebo (-0.12). Those patients who had a reduction in polyp scores of at least 1 point ("responders") observed a sustained effect over nearly 1 year. Thus mepolizumab had a clinically relevant and, in selected patients, long-lasting effect on nasal polyposis refractory to both topical GCSs and sinonasal surgery. Mepolizumab was well tolerated, with common cold-like symptoms being the most frequent adverse events.

An international multicenter study including 105 patients treated with mepolizumab or placebo has just been finalized.

The primary objective of this randomized controlled trial was to define the effect of mepolizumab in reducing the need for surgery based on predefined endoscopic polyp and symptom scores after 6 months of dosing. It is currently unclear whether anti-IL-5 hmAbs will be registered for the indication of nasal polyposis.

ANTI-IL-4/IL-13 hmAbs

In addition to IL-5, IL-4 and IL-13 could prove to be targets for hmAbs. These cytokines signal through 2 different receptors that partly overlap in their functions, and they both contain the α subunit of the IL-4 receptor (Fig 4). The type 1 receptor that can only be activated by IL-4 is mainly expressed on lymphocytes and regulates differentiation of those cells. The type 2 receptor that is activated by IL-4 and IL-13 is expressed by a multitude of cells and has different functions, among them mucus secretion, which is typically abnormal in patients with nasal polyposis. Dupilumab is a fully human mAb against the α subunit of the IL-4 receptor and can inhibit the effects of both IL-4 and IL-13.⁴⁹

Because IL-4 and IL-13 also play a role in the pathogenesis of nasal polyposis, we performed a double-blind, placebo-controlled randomized study on the effectiveness and safety of dupilumab in patients with CRSwNP with or without concomitant asthma with polyp scores of at least 5 of 8 points.⁵⁰ Sixty patients with bilateral nasal polyposis refractory to GCSs were observed for 4 weeks during topical GCS treatment and then treated either with 300 mg of subcutaneous dupilumab per week (loading dose, 600 mg) or placebo for 16 weeks. In the verum group the polyp score significantly decreased compared with that in those receiving placebo, and the CT score according to Lund and Mackay was significantly reduced versus that in those receiving placebo; both arms were receiving daily mometasone furoate nasal spray. The Sino-Nasal Outcome Test and the University of Pennsylvania Smell Identification Test smelling tests revealed clinical and statistically significant effects compared with placebo. More than half of the patients responded with a reduction of the polyp score of at least 2 points (about similar to the effectiveness of 3 weeks of oral application of GCSs). Symptoms, including nasal obstruction, rhinorrhea, and smell disturbance, significantly improved in the treatment group; peak nasal flow

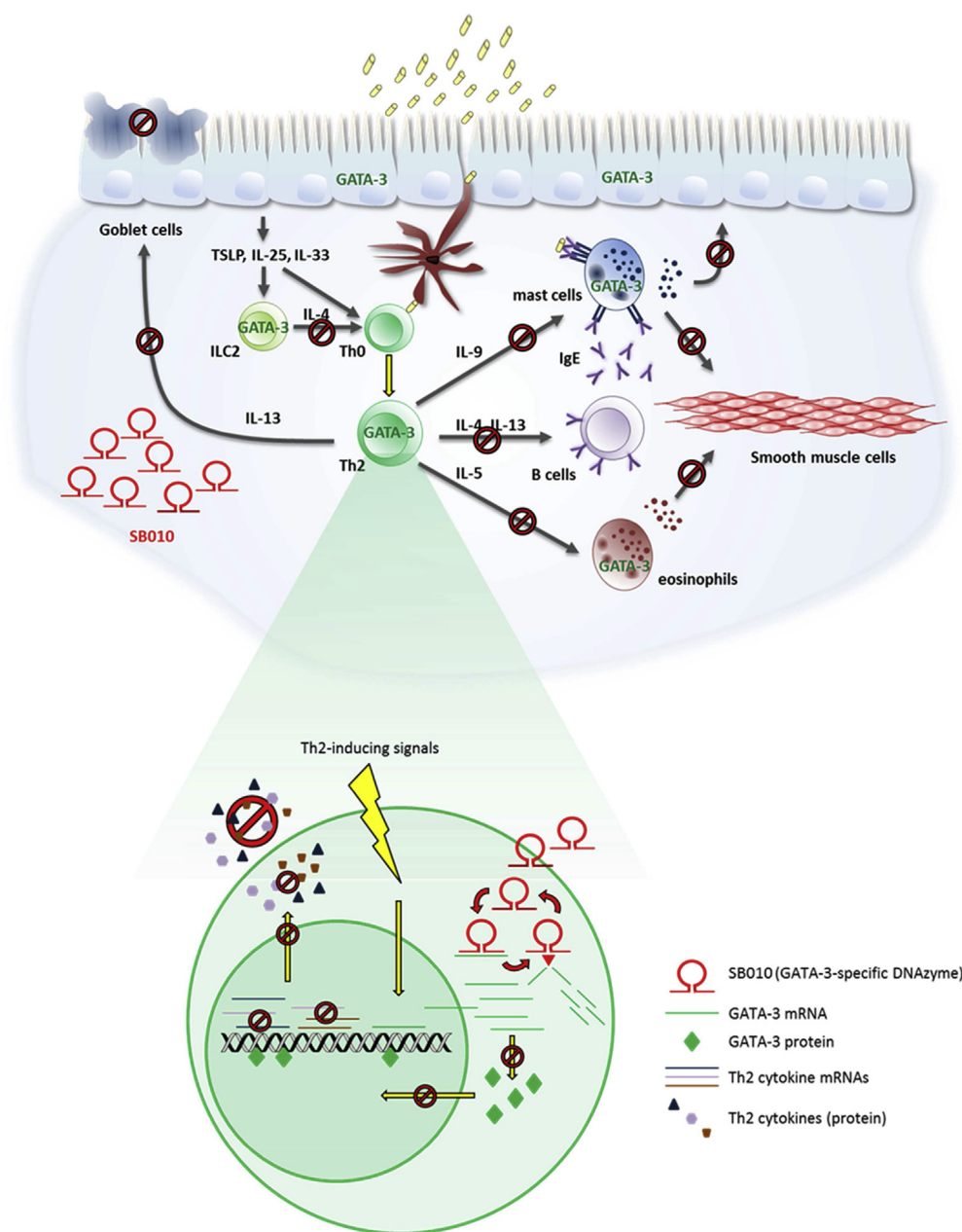


FIG 5. Role of GATA-3 and principles of DNAzyme therapy. Used with permission from Krug et al.⁵³

measurements improved by 60%. The drug was well tolerated, with the most frequently reported adverse events being nasopharyngitis, injection-site reactions, and headache. A follow-up over 16 weeks during topical GCS treatment showed a continuous improvement/maintenance of the dupilumab effect up to 2 months off treatment, which slowly decreased thereafter.

Asthmatic patients achieved significantly improved pulmonary function and asthma control test results in comparison with placebo. Concentrations of biomarkers of eosinophilic inflammation (serum IgE, thymus and activation-regulated chemokine, and eotaxin-3) were also significantly reduced in serum; in contrast to anti-IL-5, however, the absolute number of eosinophils in the blood did not decrease.

The results of this study are consistent with previous investigations in patients with severe asthma and atopic dermatitis

and confirm the potential of dupilumab to inhibit T_H2 -induced inflammation and consecutive symptoms and complaints.^{49,51}

APPROACHES TO COME

When reviewing the hmAbs in studies of asthma, other candidates are likely to be tested in proof-of-concept studies in patients with nasal polyposis, including anti-IL-4, anti-IL-13, and anti-thymic stromal lymphopoietin hmAbs. Although the development of biologics is very promising and without a doubt serves as proof of concept for future treatments, there are still problems to solve, such as the necessity of regular systemic applications with the risk of notable side effects and the probably high costs of products. For instance, the question of omalizumab possibly increasing the risk of malignant diseases could only

recently be disproved.⁵² Although relief of the total burden of comorbid T_H2 -driven disease might benefit from systemic treatment, it would be preferable to use local administration for isolated airway disease, minimizing the systemic risks and reducing the drug load and probably the costs.

Representing such local approaches, 2 different candidates in development will be discussed briefly here, which have already been tested in human subjects and provided evidence of clinical effectiveness on mucosal surfaces.

GATA-3 DNAZYME

The T_H2 endotype is characterized by the predominance of activated T_H2 cells that synthesize and release the cytokines IL-4, IL-5, and IL-13. The expression and production of those cytokines is controlled by the transcription factor GATA-3, which is relevant for the differentiation and activation of T_H2 lymphocytes and also expressed in the newly discovered type 2 innate lymphoid cells; GATA-3 might be considered the “master switch” of T_H2 -associated diseases (Fig 5). GATA-3 is overexpressed in patients with nasal polyps, asthmatic patients, and patients with atopic eczema. By reducing levels of T_H2 -related cytokines, a deactivation of the master switch would also inhibit consecutive pathways, such as IgE production.

An innovative approach could possibly deactivate all T_H2 cytokines through blockage of the transcription factor GATA-3, consecutively preventing IgE production and tissue eosinophilia.⁵⁴ Because GATA-3 is expressed intracellularly, so-called silencing techniques are applied; molecules would have to penetrate into the target cells (T_H2 and type 2 innate lymphoid cells). A GATA-3 DNAzyme has been developed, consisting of a DNA molecule that docks to the GATA-3 RNA and destroys it by means of a catalytic enzyme. The DNAzyme hgd40 is stable, highly specific, and easy to apply through inhalation or spray to the mucosa. In our laboratory we showed that the GATA-3 DNAzyme is taken up by mucosal T cells without further manipulation and significantly reduces expression of GATA-3 RNA, which leads to a decrease in IL-5 protein production.⁵³ Applied in an asthma model in human subjects, hgd40 led to a significant reduction of the immediate and late allergic phases, as well as markers associated with T_H2 reactions. The GATA-3 DNAzyme has high potential in the treatment of T_H2 -associated diseases, including nasal polyposis.

GENETICALLY MODIFIED *LACTOCOCCUS LACTIS*

Instead of complex antibodies that have to be produced and humanized in expensive processes to be applicable systemically, it is also possible to choose approaches in which proteins or their derivatives, such as nanoproteins, are produced directly on the mucosa by nonpathogen bacteria. This approach led to the development and production of genetically modified *L lactis*, which has demonstrated preclinical and clinical applicability for a series of diseases.⁵⁵ Advantages are local application and the possibility of producing several therapeutically effective proteins by using genetically modified *L lactis*.

SUMMARY

It has become obvious that the therapeutic approaches pursued up to now, as they are summarized in current European and US guidelines, do not lead to long-term control of the symptoms or risks of recurrence and comorbid asthma in a subgroup with severe persistent disease. This subgroup has recently been identified as a type 2 immune response, with increased expression of the transcription factor GATA-3; increased production of IL-4, IL-5, and IL-13; and increased local production of IgE characteristic of this immune response. At the same time, these indicate innovative targets for intervention. The targets are not limited to a specific clinical entity but might encompass different diagnoses (eg, CRSwNP, AERD, and AFRS).

Biologics have opened a new dimension of effectiveness in comparison with oral corticosteroids because permanent application of oral corticosteroids would undoubtedly lead to health deterioration that cannot be accepted. Repeated sinus surgeries with increased risks of complications are likewise not an option in these patients.

In patients with severe T_H2 inflammation with a high probability of recurrence after surgery and comorbid asthma and in whom symptoms cannot be controlled by those means, an alternative approach should be offered. For those patients, biologics are a valuable alternative because they can control symptoms of the upper and lower airways. Currently, no hmAb is available for the indication of nasal polyposis; however, asthmatic patients might benefit from a significant improvement of asthma and polyp control. It is a question of time until hmAbs will be available for patients with severe CRSwNP; however, it is unclear whether one hmAb is more effective than others in the treatment of this disease or more suitable for a subgroup of patients with severe disease. Although hmAbs serve as proof of concept and hopefully will be registered for nasal polyposis, the next generation of interventions is already on its way.

LIST OF KEY CONCEPTS AND THERAPEUTIC IMPLICATIONS RELATED TO THE TOPIC

- Pharmacotherapy and surgery show limitations in controlling severe CRSwNP (frequent recurrence and asthma comorbidity).
- Severe CRSwNP is mostly characterized by a T_H2 bias, and up to 50% of subjects have IgE antibodies to *S aureus* enterotoxins.
- The T_H2 cytokines IL-4, IL-5, and IL-13 and IgE served as targets for innovative interventions, mostly hmAbs (biologics).
- Proof-of-concept studies have been performed with omalizumab (anti-IgE), reslizumab and mepolizumab (anti-IL-5), and dupilumab (anti-IL-4 receptor α).
- None of these hmAbs have been registered for the indication of nasal polyposis yet, and it is unclear whether any of the hmAbs are superior to others for all or a subgroup of patients with severe CRSwNP.
- Future approaches, including silencing techniques and production of antagonistic proteins by apathogenic bacteria, are on the horizon.

What do we know?

- CRS can be differentiated into endotypes with characteristic pathomechanisms.
- CRSsNP is often treated adequately with surgery; CRSwNP tends to develop recurrence in a high percentage of subjects over longer than 10 years and is associated often with comorbid asthma.
- Disease recurrence and asthma comorbidity are associated with T_H2-biased inflammation and IgE formation; in patients with severe disease, the presence of IgE antibodies to *S aureus* enterotoxins is characteristic.
- Oral GCSs are associated with important side effects, preventing long-term or repeated use.
- Anti-IL-5, anti-IgE, and anti-IL-4 receptor α (affecting both IL-4 and IL-13 pathways) have shown clinical efficacy in proof-of-concept studies.

What is still unknown?

- Would biomarkers in serum help to predict prognosis after surgery and comorbidity and thus define patients with severe disease or select patients likely to respond to specific treatment approaches?
- Is one of the innovative hmAbs better than others or more suitable for a specific subgroup of patients?
- What are possible dosing regimens for long-term use for the hmAbs, and are longer intervals and lower dosages after an initial high dosing phase appropriate?
- Are local therapies possible with further innovative approaches, such as silencing techniques?
- Are innovative approaches needed and possible for other than T_H2-related cytokines?
- How important is the neutrophilic component we find in nearly all polyps?

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