

Biotherapeutics in Chronic Rhinosinusitis with and without Nasal Polyps



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In western countries, 85% of chronic rhinosinusitis with nasal polyp disease reveals a type 2 inflammatory pattern with expression of IL-4, -5, and -13 as well as increased concentrations of IgE, whereas chronic rhinosinusitis without nasal polyps merely expresses these biomarkers. The degree of type 2 inflammation furthermore is associated with disease severity, asthma comorbidity, and recurrence of disease after surgery. Therefore, these biomarkers also form the targets for innovative therapeutic approaches such as monoclonal antibodies directed against IgE, IL-5, and IL-4 receptor alpha, blocking the activity of IL-4 and -13. Having demonstrated efficacy in severe asthma, the antibodies have been tested in proof-of-concept studies in patients with nasal polyposis with or without asthma, and have demonstrated their potential to reduce nasal and sinus nasal polyp burden monitored by nasal endoscopy and computed tomography scanning, and to improve typical symptoms. No biomarkers have been identified to select subjects for therapy, to predict response to a specific drug, or to monitor treatment success, which is best documented by nasal polyp score and symptoms. Phase 3 studies are currently in preparation or running, which aim to demonstrate efficacy in larger patient populations and to achieve registration for the indication nasal polyps. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:1512-6)

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With the introduction of precision medicine, also termed personalized medicine, a new era has rapidly developed specifically in oncology, but in the last 5 years also in airway inflammatory diseases^{1,2} such as cystic fibrosis, asthma, rhinitis, and chronic rhinosinusitis (CRS). CRS and asthma are closely related to each other in many aspects, and it is therefore no surprise that not only pathomechanisms but also therapeutic principles are similar in both sections of the airways. With the interest of pharma industry focusing on asthma, a subgroup of CRS with nasal polyposis (CRSwNP) also profits from new knowledge derived from proof-of-concept (PoC) studies and from the aspect of having innovative therapeutic possibilities in patients with severe CRSwNP, in whom topical corticosteroids could not control disease, systemic glucocorticosteroids (GCS) are not recommended as long-term treatment, and first and even repeated sinus surgery does not offer a solution. From those patients, in whom no other options are available, the indication needs to be extended to balance against the risk of adverse events from repeated and long-term systemic GCS, and the complications and discomfort possibly resulting from—specifically repeated—sinus surgery.

It gets clear that a better understanding of those patients not controlled by current approaches is necessary, which should result in the development of diagnostic means to recognize those patients early and spare them from unsuccessful surgery. These diagnostics could also help to optimize the treatment and to achieve long-term control from early on. In other patients, in whom one or several surgical procedures have been performed already without success, or who already suffer from combined airway disease, the decision for innovative biologics still needs certainty in terms of likelihood of success or response to the treatment. As we will see, this certainty may come from clinical phenotyping alone, but biomarkers again might be helpful to choose the best of several drugs for an individual patient. At the moment, however, with first studies in phase 3 running, an indication for biologics in the indication CRSwNP or nasal polyposis has not been provided yet.

Care pathways need to be developed that include the phenotypes and endotypes of the disease, building up on the experience of an individual patient with former treatments and their outcomes, which finally will position biologics in the treatment proposal according to their therapeutic efficacy, possible adverse events, but also costs and patient comfort versus other approaches, specifically systemic GCS and surgical procedures. The recent GINA guidelines³ have developed approaches for severe asthma positioning biologics above oral GCS long-term therapy, despite the costs, but for the advantage and comfort of the patients. Similar decisions have to be taken for patients with CRSwNP. Different from

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
GCS- Glucocorticosteroids
PoC- Proof of concept
QoL- Quality of life

severe asthma, surgery in CRSwNP does play a prominent role in the treatment, and is often favored by operating ENT surgeons over other treatment options for many reasons. It will need intense education of and discussion with the stakeholders involved in the management of patients with CRSwNP to come to the best therapeutic plan including the evaluation of the benefits of surgical versus nonsurgical approaches like biological treatment.

We here aim to discuss phenotypes and endotypes of CRS as a prerequisite for understanding patient selection, describe the unmet need for patients with chronic rhinosinusitis without nasal polyps (CRSsNP) and CRSwNP, discuss the current information derived from PoC studies, define the patients likely to profit from biologics, and outline the current deficits in optimal patient selection and biomarker follow-up. Although some biotherapeutics have demonstrated efficacy in CRSwNP, there still are 2 to 3 years of clinical studies necessary before the first will come to the market in this indication. Biotherapeutics in CRS without nasal polyps are currently not developed, and targets for such an approach are not defined. The role of eosinophils in CRSsNP is unclear.

CLINICAL PHENOTYPES AND ENDOTYPES

CRS is an umbrella term, including different clinical phenotypes that are currently differentiated on clinical signs (uni- or bilateral nasal polyps or pus in the middle meatus in nasal endoscopy, dense material on the computed tomography [CT] scan suggestive for fungus), history (reaction to allergen, aspirin) or challenge tests (allergen challenge, aspirin challenge), skin prick tests (allergens), serum measurements (immunoglobulins, IgE to *Aspergillus fumigatus*), or genetic analysis (cystic fibrosis). From these, diagnoses such as CRSsNP, CRSwNP, allergic fungal rhinosinusitis (AFRS), CRSwNP with asthma, CRSwNP with aspirin exacerbated respiratory disease (AERD), and others are derived. However, many of these clinical phenotypes may share the same pathomechanisms (type 2 inflammation in CRSwNP, AFRS, AERD), whereas a clinical sign such as nasal polyps may have clearly different pathomechanisms (nasal polyps in CRSwNP vs cystic fibrosis). These considerations ask for a better understanding of the underlying biomechanical principles.

Furthermore, within a phenotype such as CRSwNP, considerable differences in terms of pathomechanisms have recently been described even in patients of the same ethnic background,⁴ describing a non-type 2, moderate type 2, and severe type 2 inflammation, also expressing IgE antibodies to *Staphylococcus aureus*, in CRS European patients. Whereas asthma comorbidity is low in the non-type 2 endotype, it may reach 70% in the severe type 2 endotype⁴; also, recurrence rates are low in the first, but high in the latter endotype. Inflammatory endotypes thus

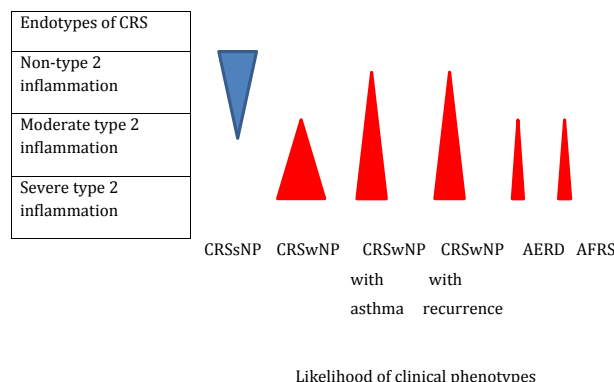


FIGURE 1. Pathophysiologic endotypes and clinical phenotypes and their relationships: Whereas CRSsNP only partially represents a moderate type 2 inflammation, CRSwNP with or without asthma or recurrence, AERD, or AFRS all mostly represent type 2 inflammatory reactions. *AERD*, Aspirin exacerbated respiratory disease; *AFRS*, allergic fungal rhinosinusitis; *CRS*, chronic rhinosinusitis; *CRSsNP*, CRS without nasal polyps; *CRSwNP*, CRS with nasal polyps.

correlate with disease severity and allow recognizing novel therapeutic targets for biologics such as type 2 cytokines and IgE (Figure 1).

It also has been shown that the distribution patterns of these endotypes may differ significantly from Europe to China and from Australia to Japan, whereas the associations with comorbid asthma and disease recurrence per endotype are stable findings.⁵ For example, 85% of tissue expresses relevant concentrations of IL-5 in European patients with CRSwNP, but only 15% of patients with CRSwNP in central China show IL-5 positive polyp tissues. Consequently, asthma comorbidity in European patients with CRSwNP is significantly more frequent than in Chinese patients. It is therefore mandatory to understand the distribution of endotypes in the region of personal practice, and to search for biomarkers that allow endotyping of CRS without the necessity of nasal biopsies.

UNMET NEEDS IN CRSwNP

Although European and US guidelines for CRS provide treatment algorithms, a subgroup of patients with CRSwNP remains uncontrolled over longer time even with continuous use of topical GCS, courses of antibiotics and oral GCS, and sinus surgery. A recent study recruiting patients with CRSwNP from tertiary referral academic hospitals in North America concludes that “polyp recurrence is common after ESS (sinus surgery) with control of polyps up to 18 months found in approximately 60% to 70% of patients” only.⁶ Another recent study in a European academic center on the level of control at a mean interval of 3 years after sinus surgery showed uncontrolled CRS in up to 45% of patients after sinus surgery.⁷ In a follow-up study over 5 years, approximately 25% of patients in our clinic in Ghent needed a second surgery for nasal polyp recurrence⁸; the tissue biomarkers predicting recurrence and need for revision surgery were type 2 cytokines and markers, including IL-5, IgE, and eosinophil cationic protein. In a prospective follow-up study over 12 years, we demonstrated that approximately 80% of patients with

TABLE I. Comparison with signatures of biotherapeutics studied in nasal polypsis

	Omalizumab	Mepolizumab	Dupilumab
No. of patients (verum/placebo)	24 (15/8)	30 (20/10)	60 (30/30)
Dosing	For severe asthma	2 × 750 mg	600/300 mg/wk
Asthma	100%	43%	58%
Former surgery	82%	77%	58%
INCS during study	No	No	MFNS
Timing endpoint	16w	8w	16w
Result NP score over placebo	−2.5	−1.3	−1.6/−2.3 in asthmatics
CT scan	LMK −4.1	Percentage improvement >50% vs <20%	LMK −8.8
Symptoms significantly better with verum	Lower and upper airway symptoms	Upper airway symptoms (trends only)	Lower and upper airway symptoms, PNIF, UPSIT
Significant changes in QoL	SF36 (physical), RSOM-31, AQLQ (vs baseline)	—	SNOT22
Significant effects on asthma	—	—	ACQ5, FEV1% predicted
Biomarkers reduced	—	Blood eosinophils, ECP	Serum IgE, TARC, eotaxin 3
Frequent drug-related adverse events	Nasopharyngitis, headache	Nasopharyngitis	Nasopharyngitis, headache, injection site reactions

ACQ5: Asthma Control Questionnaire 5; AQLQ: Asthma Quality of Life Questionnaire; CT: computed tomography; ECP: eosinophil cationic protein; FEV1: forced expiratory volume in 1 s; INCS: intranasal corticosteroid spray; LMK: Lund-Mackay score; MFNS: mometasone furoate nasal spray; NP: nasal polyp; PNIF, peak nasal inspiratory flow; QoL, quality of life; RSOM-31, rhinosinusitis outcome measure 31; SF36, short form 36; SNOT-22, sinonasal outcome test—22 questions; TARC, thymus and activation regulated chemokine; UPSIT, University of Pennsylvania Smell Identification Test.

CRSwNP developed recurrence and approximately 37% needed at least one revision surgery after the initial intervention.⁹ In a European GALEN sinusitis cohort study performed in 8 academic centers, approximately 25% of the patients recruited with nasal polyps had 4 or more surgeries in the history, although they were treated with topical GCS and courses of oral GCS and antibiotics continuously over years (unpublished). This clearly indicates that sinus surgery—at least with the currently performed surgical techniques—is not sufficient to maintain control in a subgroup of patients with CRSwNP with severe type 2 inflammation, albeit additional anti-inflammatory treatment. On the other hand, the continuous use of oral GCS with median daily doses of prednisolone of 5 mg over years will lead to significantly higher rates of type 2 diabetes, osteoporosis, dyspeptic disorders (including gastric/duodenal ulceration), and cataracts.¹⁰ Furthermore, in patients with severe CRSwNP and several oral GCS bursts per year, 43% developed osteoporosis and 49% secondary adrenal insufficiency.¹¹ Thus, neither repeated surgery nor oral steroid long-term use is the option for those patients with severe inflammation and massive polyp burden. In addition, with biotherapeutics being available in the future, providing efficacious and safe alternatives to current treatments, patients will ultimately vote for biologics treatment.

Biotherapeutics in clinical trials

There are 4 monoclonal antibodies that have been studied in CRSwNP so far: omalizumab, reslizumab, mepolizumab (all investigator initiated studies), and dupilumab.¹² Of those, reslizumab is currently not further developed in this indication, whereas phase III studies are running or starting shortly for the other 3. For omalizumab, being on the market for the treatment of severe asthma since more than 10 years, a large body of safety data and real life data are available; although a black box warning has been issued for anaphylaxis, and an increased risk for cancers has only recently been cleared, omalizumab is considered safe in daily practice.¹³ Mepolizumab and dupilumab^{14,15} both showed good tolerability in the PoC studies, without serious adverse events related to the drug. Injection site reactions, nasopharyngitis, and headache were the most frequent symptoms.

Eligible patients were aged 18 to 65 years with bilateral nasal polyps despite intranasal GCS treatment (Table I); prior surgery was accepted, if not performed, in the last months before surgery. Patients in all studies had a nasal polyp score of more than 5 (out of a maximum score of 8). All patients were also symptomatic, with nasal obstruction and loss of smell being most prominent, although only one of the trials had symptoms as inclusion criterion. Any asthma—excluding severe asthma—was present in 43% to 100% of the study subjects; all subjects in the omalizumab trial needed to fulfill this criterion.¹⁶ Also, 58% to 82% of the subjects had prior surgery for CRSwNP. The number of patients was rather small, with maximally 30 patients per arm; the fact that the nasal polyp score was considered the primary outcome criterion and this variable normally does not decrease in placebo-treated patients in contrast to symptom scores and quality of life (QoL) measures made it possible to achieve significant results despite the low number of patients. However, because of the different populations included (eg, with or without asthma), the comedication, the length of treatment period, and the small

TABLE II. Unmet needs in CRSwNP

Endotyping:
Differentiation of CRS into endotypes: relevance of non-type 2 endotypes, differentiation of pathways within type 2 inflammation
Biomarkers:
Serum biomarkers for moderate and severe type 2 inflammatory reactions
Serum biomarkers to select biotherapeutic drugs, predict and monitor therapeutic responses
Treatment schedules:
Phase 3 studies to determine optimal dosing from start to efficacy plateau
Studies on the optimal dosing for long-term treatment in responders
Care pathways:
Elaboration of integrated care pathways for patients with CRSwNP disease
Definition of indications and contraindications for oral glucocorticosteroid use, sinus surgery
Integration of biotherapeutics in the current treatment flow

CRS, Chronic rhinosinusitis; CRSwNP, CRS with nasal polyps.

numbers of trial participants, comparisons between trials should be interpreted with great care. As we have discussed before, asthma comorbidity and prior surgery may increase the likelihood of a type 2 inflammatory reaction, which might be decisive for the response to treatment independent of any biomarker.

For 2 of the trials, the bilateral nasal polyp score was measured as the primary outcome at 16 weeks after continuous treatment; for mepolizumab, only 2 injections were given, and the treatment period was 8 weeks only. For the mepolizumab and omalizumab trials, the patients had to omit nasal GCS treatment, whereas they were continuously treated with mometasone furoate in the dupilumab trial. Given all these differences, the patients (all asthmatics) receiving omalizumab experienced a similar reduction of the nasal polyp score of more than 2 points as the patients with asthma in the dupilumab trial. The effect of mepolizumab was smaller, most likely due to the shorter treatment duration. Nasal polyps, consisting of an inflammatory and a remodeling component, need several weeks to shrink if only inflammation is addressed—different from oral GCS addressing both components at the same time. The effects of omalizumab and dupilumab on the polyp score were in the same order as those observed at the peak of a 3-week oral GCS treatment.¹⁷ Thus, we can state that the effects of biotherapeutics certainly are of relevance in a clinical setting, specifically as the effects can be maintained over years and thus much longer—and safer—than those temporarily achieved by oral GCS. Open posttreatment observation periods in these small trials performed so far revealed that it may take several months after end of treatment until polyps are regrown to former size.

The changes in nasal polyp scores were also reflected in a reduction of polyp burden in the sinuses as measured by CT scan, using the Lund-Mackay scoring in 2 of the studies. The typical symptoms of nasal polyposis, including nasal and bronchial symptoms, and asthma QoL or control questionnaires ameliorated in those patients with comorbid asthma (this parameter was not monitored in the mepolizumab study). Specifically, smell improved in all trials based on questions, but also based on objective measurements (University of Pennsylvania Smell Identification Test) in the dupilumab study.

To summarize, we can state that biotherapeutics have the potential to significantly reduce polyp score and CT scan opacification, as well as all symptoms of disease (including loss of smell) and asthma burden in those patients with comorbid disease. This likely also results in effects on lung function, although more studies are necessary here. Specifically patients with comorbid asthma may thus benefit additionally, but efficacy in nasal polyposis is not limited to those patients. Furthermore, those biotherapeutics work in patients who already have undergone surgery and thus could offer those patients with disease recurrence an alternative; however, more data about efficacy in long-term use need to be collected from the phase III studies. With the tolerability experienced so far, biotherapeutics may also be used long term without relevant adverse events or contraindications, providing solutions to the severe patient population. In perspective of the long-term side effects of oral GCS use and the risk of potentially severe complications due to sinus surgery, medical doctors and patients together should get the right to choose the best option based on the patients' former treatment approaches and outcomes, but also risks associated with treatment approaches. We also need to understand that for some severe patients, there is no other option left when oral GCS and former surgery are not offering long-term control, are contraindicated or may be associated with considerable risks, or patients do not accept those interventions anymore (Table II).

For the moment, no single biotherapeutic is registered for the treatment of CRSwNP yet. Patients receiving omalizumab or mepolizumab for the treatment of severe asthma however may already benefit. In patients with late-onset asthma, the nose should be investigated for nasal polyps.

Biomarkers for selection of drug and outcome monitoring

It is obvious that biotherapeutics targeting IgE, IL-5, or IL-4 and IL-13 should only be applied in nasal polyp disease, in which those biomarkers are expressed and contribute to the pathophysiology. This applies for approximately 85% of disease in central Europe, but may differ considerably in other regions in the world.⁵ As high levels of these biomarkers are also associated with more severe local disease, comorbid asthma, and recurrence after surgery, those clinical observations could help to identify potential candidates in terms of relevant pathomechanism and severity of disease. Furthermore, biopsies for biomarkers in the tissue could theoretically be used, but neither the biopsy nor the measurement of the markers is practical and established. Nasal secretion could serve as a surrogate, but no studies have so far been performed to determine its role as a diagnostic tool in nasal polyps. Search for biomarkers in serum is currently running using a large European cohort, the GALEN sinusitis cohort; first results are promising, using several biomarkers to differentiate no from moderate and severe type 2 inflammation in CRSwNP.⁴

No biomarkers are currently known to select between possible strategies; neither cutoffs for blood eosinophils to support the use of an anti-IL5 strategy, nor tests for inhalant allergens or total IgE in serum have been demonstrated to predict response to anti-IgE therapy. The frequently proposed differentiation of patients with nasal polyps in nonallergic subjects with high blood eosinophils to choose anti-IL-5, and allergic patients for anti-IgE approaches, is not supported by evidence. Approximately 60% of the mepolizumab-treated patients responded to the treatment

independent of blood eosinophil counts, and omalizumab worked at least as good in nonallergic compared with allergic nasal polyp subjects.¹² It is known that mepolizumab rapidly reduces blood eosinophil counts, and that omalizumab diminishes free IgE antibodies, but it remains unclear which biomarker is important for the clinical effect in nasal polyps. Dupilumab, blocking IL-4 and IL-13, reduced IgE and chemokines in serum, and although it did not diminish blood eosinophil counts, it significantly reduced eosinophil markers in nasal tissue and secretions (unpublished). Dupilumab therefore targets type 2 inflammation at several aspects. The question of common biomarkers for the selection and monitoring of biotherapeutics remains yet to be answered. Furthermore, no currently used biomarkers such as blood eosinophils or total serum IgE have been demonstrated to help in the selection of or predict responses to biotherapeutics.

The role of biotherapeutics in the treatment of patients with nasal polyps

With the phase III studies accomplished, possibly several biotherapeutics will become available for patients with severe nasal polyps. Care pathways need to be elaborated positioning the new drugs in the treatment algorithms currently covering topical and short-term systemic oral corticosteroids as well as antibiotics for exacerbations or long-term use (see Table II). Once biomarkers are available to recognize the individual patient's endotype and predict the prognosis in terms of achievable control of disease by surgery and the risk of developing comorbid asthma, a decision for the use of a biological drug may be taken early in the disease course. Until then, it will be the patients in whom control cannot be achieved by either surgery or topical and/or oral GCS, or in whom such treatment is contraindicated or rejected. For an optimal decision-making process, however, the term "surgery" needs to be differentiated; it has become obvious over the past few years that the extent and aims of surgery also need to be elaborated according to the endotypes of CRS rather than the pure extension of opacification on the CT scan. Furthermore, a better understanding of the side effect risks for oral GCS needs to be achieved, if they are to be maintained in the treatment algorithm. Finally, the patient's voice needs to be heard in the choice of treatment possibilities, once available. For many patients with severe disease, which was left uncontrolled with the current surgical and pharmacological possibilities, biotherapeutics soon will offer new and significant treatment options.

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