

Endotypes of chronic rhinosinusitis: Impact on management



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Following the trend in asthma, endotypes for chronic rhinosinusitis with nasal polyps have been established, with type 2 immune reactions representing >80% of nasal polyp cases in Europe and the United States. Endotyping is without doubt useful to predict the natural course of disease, to determine pharmacotherapy and the extent of surgery, and lately also to select patients for treatment with type 2 biologics. However, with the opening of this new era of treatment, limitations of the current possibilities in subgrouping patients also became apparent, as (1) mixed endotypes often can be found and (2) predictions as to the best biologic to be used in an individual patient are not yet possible. Some of the questions to address in the near future are discussed. (*J Allergy Clin Immunol* 2020;145:752-6.)

Key words: chronic rhinosinusitis, nasal polyps, endotypes, type 2 inflammation, surgery, biologics

Endotyping of chronic rhinosinusitis (CRS) is a recent development, which we here summarize briefly. In 2013, a PRACTALL document was elaborated in a cooperative effort between the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology and published in the *Journal of Allergy and Clinical Immunology*.¹ The document described the limitations in the knowledge on pathomechanisms as a major obstacle in understanding the causes of CRS and improving its treatment. Although clinically relevant CRS phenotypes have been defined by observable characteristics and treatable traits, such as the presence or absence of nasal polyps, it was clear that phenotypes may be based on different underlying pathomechanisms, which may provide an innovative and relevant differentiation

Abbreviations used

CLC: Charcot-Leyden crystal
CRS: Chronic rhinosinusitis
CRSsNP: Chronic rhinosinusitis without nasal polyps
CRSwNP: Chronic rhinosinusitis with nasal polyps

of disease subgroups: endotypes based on biomechanistic principles. At that time, several smaller proof-of-concept studies using innovative treatments or biologics in CRS with nasal polyps (CRSwNP), including reslizumab, mepolizumab, and omalizumab, had already been published,²⁻⁴ and other studies with mAbs were to be performed. These studies, all initiated at Ghent University, made use of the fact that in Belgium more than 80% of nasal polyps show a type 2 signature and thus may respond to the treatment.⁵

Another source for the development of endotypes was the natural course of the disease in terms of the involvement of the lower airways, mostly described as asthma comorbidity. This involvement is typically late in onset and increases with the severity of inflammation. Endotypes of asthma have been described recently, providing new insights into key pathogenic mechanisms for a complex, heterogeneous disease.⁶ Also, asthma often is characterized by type 2 inflammation; the type 2-high endotype can have either an allergic or a nonallergic background and is typically characterized by some degree of eosinophilic airway inflammation.⁷ Aspirin-exacerbated respiratory disease has also long been recognized as a unique asthma phenotype carrying a type 2 signature. Increased exhaled nitric oxide and blood eosinophil counts are biomarkers for type 2 endotype bronchial asthma, specifically useful in the identification of severe asthma with frequent exacerbations, which occurs in about a third of the population of individuals with asthma.⁸ Other comorbidities may further characterize type 2 airway disease.⁹ Thus, endotyping of CRS helps in understanding and predicting the natural course of disease and in choosing the adequate treatment, from pharmacotherapy to surgery and biologics. Fig 1 summarizes strong and possible indicators for type 2 immune reactions in CRS. As indicated in Fig 1, we do not necessarily need blood or serum biomarkers for identification of a type 2 immune response; the presence of late-onset asthma—and even more so, of nonsteroidal anti-inflammatory drug-exacerbated respiratory diseases with the asthma—increases the likelihood of a type 2 endotype to near to 100%. It was thus the right time point to introduce into clinics the concept for the upper airways also, and to

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How to identify Type 2 CRSwNP	Likelihood of Type 2 CRSwNP*
1) Clinical traits	
• Bilateral CRSwNP without comorbidity	> 80%
• Allergic sensitization	> 90%
• One or more effective oral GCS courses in last year	> 90%
• Comorbid late-onset asthma	> 90%
• N(SAID)-ERD	100%
• Former surgery with tissue eosinophilia (histology)	100%
2) Biomarkers	
Blood eosinophils > 150/ μ l	> 90%
Serum IgE high, polyclonality	> 90%
Serum SE-IgE positivity	100%

* data from the Upper Airways Research Laboratory data base, C. Bachert, Ghent University

FIG 1. How to identify type 2 CRSwNP. GCS, Glucocorticosteroid; N(SAID)-ERD, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease.

develop biomarkers and individualized care pathways for CRS based on a differentiation into type 2 and non-type 2 endotypes. In the past 5 years, more than 60 publications on CRS with the term *endotype* in the title have been written.

The first analysis of CRS endotypes, primarily based on measurements of cytokines and mediators in the sinus mucosa and secondarily related to clinical traits, was published in 2016.¹⁰ This analysis showed that asthma comorbidity and recurrence of disease after surgery were both associated with increased mucosal concentrations of IL-5, eosinophil cationic protein, IgE, and *Staphylococcus aureus* enterotoxin–specific IgE, undoubtedly reflecting type 2 inflammation. The Chicago group added to these findings that loss of smell and “allergic mucin” were significantly associated with presence of the type 2 endotype¹¹; whereas loss of smell is a frequent sign of severe polyposis, allergic mucins affects only a small population.

Type 2 inflammation is characterized by the activation of T helper type 2 cells and innate lymphocyte cells,^{12–14} producing the key cytokines IL-4, IL-5, and IL-13. Epithelial cells triggered by *S aureus* and releasing IL-33 may initiate the flow of events.^{15,16} It is necessary to mention that “type 2” often is not as “pure” as is often thought. The typical sticky “allergic mucin” is most likely caused by the release of eosinophil extracellular traps containing not only DNA and major basic protein but also galectin-10, resulting in the deposition of Charcot-Leyden crystals (CLCs).^{17,18} These CLCs, however, induce a strong neutrophilic infiltration on their own, adding to the inflammatory load of the mucosa.¹⁹ In less severe inflammation, INF- γ and IL-17 may also induce neutrophilic inflammation side to side with the presence of eosinophil granulocytes.^{20,21} However, the fact that more than 80% of bilateral nasal polyps—and thus the vast majority—are type 2 with or without comorbid type 1 or 3 inflammation¹⁰ led to the fact that non-type 2 nasal polyps were neglected in the strategy for biologic treatment. Furthermore, the identification of useful biomarkers for endotyping of CRS in daily practice seems difficult, as blood eosinophils and serum IgE are often normal in type 2 nasal polyps without asthma, and the principle of endotyping based on type 2 inflammatory cytokines in nasal secretions or tissue biopsy specimens is laborious to introduce. Importantly, although the term *type 2 inflammation* characterizes the majority of patients with nasal polyps, and obviously leads to more severe clinical expression of disease, one cannot neglect the fact that other non-type 2 mechanisms also play a role and may be very relevant in specific situations to be discussed later.

PHENOTYPES VERSUS ENDOTYPES: DECISIVE FOR TREATMENT OPTIMIZATION CONCERNING SURGERY AND BIOLOGICS

For a clinician, the symptoms of CRS include nasal obstruction, nasal secretions, postnasal drip, loss of smell, and headache or pain and/or pressure over the sinuses. Typically, patients with CRS without nasal polyps (CRSsNP) have more pain, whereas patients with CRSwNP experience loss of smell. The computed tomography scan shows opacification of 1 or several sinuses, and an experienced physician may already be able to make differential diagnostic considerations, also including fungal disease, cystic fibrosis, and other diseases. However, nasal endoscopy actually delivers the main criterion to differentiate between CRSsNP and CRSwNP: bilaterally visible nasal polyps clearly point to the diagnosis of CRSwNP, the etiology of which still has to be clarified, but the lack of visible polyps does not totally exclude the disease. In fact, nasal polyps are derived from the sinuses, as the nasal mucosa does normally show less ability to form polyps, and therefore, the term *nasal polyps* is misleading. So far, nasal polyps have been treated alike all over the world, with some local flavor to the surgery performed, and often, the surgery is no different from surgery for CRSsNP. And physicians have been more or less successful with their surgery, as polyps may be non-type 2 and do not recur, or they may be type 2 and tend to recur with increasing impact of the inflammation.¹⁰ Studies have clearly indicated variations of the type 2 versus non-type 2 distribution all over the world, with type 2 dominating CRSwNP in Europe, the United States, and Australia, but less so in China and other Asian countries.^{5,22,23}

Thus, the surgical approach to CRSwNP obviously needs to be adapted and differentiated worldwide, depending on the endotype and the degree of inflammation, and the approach needs to be different from that in CRSsNP.¹³ Avoidance of recurrence of disease is an important target, and consequently, the surgical technique needs to be adjusted to this target and thus to the disease endotype, so as not to overtreat or undertreat sinus disease. After focusing on mucociliary clearance and narrow clefts to explain CRS, the focus of surgery finally shifted to the mucosa and its inflammation. Especially unresponsive to “conventional sinus surgery” was severe type 2 CRSwNP disease, with recurrent polyps after a few months and persistent edema and symptoms.²⁴ To completely remove not only the sinus mucosa, including the polyps, but also the thickened and equally diseased mucosa next to them (Jonstam et al 2020, submitted for publication) prepared to develop polyps also, which may be a valid approach to a severe case of type 2 mucosal disease involving all the sinuses.²⁵ This approach, which has been termed *reboot*, may also involve the frontal sinuses and builds on the observation that the new mucosa growing into the sinuses from the nasal cavity shows less polyp formation. Nasal mucosa may also show type 2 bias, but it very rarely forms polyps, and thus overgrows the sinuses as a thin but functional mucosa within a few weeks after surgery. Whether this principle can be executed by many physicians, who will obviously need to be highly skilled, and will be able to maintain the polyp-free condition for many years in nearly all patients, remains to be shown. Further, the idea of endotype-based approaches to surgery has been taken up by only a few physicians, and indicative studies still need to be performed. Currently, CRSwNP and CRSsNP are often treated by following the same principles of “functional endoscopic sinus

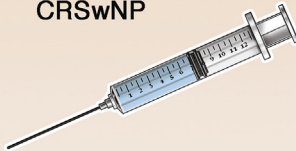
	Preferred Pharmacotherapy	Preferred Surgery	Preferred Biologics
Non-Type 2	Macrolide antibiotics	Conventional FESS	None currently in registration
Type 2	• Topical GCS, oral GCS • Doxycycline 	Extended surgery / Reboot surgery 	• Type 2 biologics (Dupilumab) • Eventually other Type 2 biologics • Depending on indication for CRSwNP 

FIG 2. Impact of type 2 endotype on CRS treatment. GCS, Glucocorticosteroid; FESS, functional endoscopic sinus surgery.

surgery.” Thus, we are undoubtedly at a turning point in the management of patients with severe CRSwNP persisting after pharmacologic treatment and even previous surgery, and endotyping is an important part in this development targeting mucosal disease.¹⁰

The first biologic for the indication CRSwNP, dupilumab, has just been registered in the United States and Europe, and its widespread use for this indication will soon follow. As already mentioned, this progress followed studies with reslizumab, mepolizumab, and omalizumab,²⁻⁴ which were recently completed by dupilumab in phase 2 and 3 studies.^{26,27} The last studies in this sequence, 2 phase 3 parallel trials with dupilumab versus placebo over 24 and 52 weeks, impressively demonstrated the shift of borders for mAbs in CRSwNP, with two-thirds of the patients reacting with a clinically significant decrease in polyp mass and symptoms and an impressively fast onset of action especially in relation to the sense of smell. Smell had already improved within the first 2 weeks, which was faster than the decrease in polyp mass, and over the course of 24 weeks anosmia turned into at least hyposmia in about two-thirds of the 76% of subjects who were anosmic at start of study. This again clearly demonstrated the role of type 2 inflammation in the induction of loss of smell, with an effect of anti-IL-4/13 (dupilumab) surpassing that of anti-IL-5 (mepolizumab) or anti-IgE (omalizumab). Type 2 cytokines have been shown to be reduced in nasal secretions under dupilumab therapy.²⁸ The effects of biologics clearly confirm the role of type 2 immune disease in the symptomatology related to CRSwNP in the majority of, but not all, patients—especially, in those not responding to the drug. How can we understand nonresponders when treating type 2 CRSwNP with the anti-type 2 drug *par excellence*? Is it possible that type 2 is not 1 entity and subgroups exist within type 2 CRSwNP? Although some patients may just need more time to react to the treatment with a decrease in nasal polyp score, or may need higher dosage at least at the start of treatment to overcome the strong inflammation, those patients who respond

to the treatment only marginally or not at all raise questions. Is it a question of dosing only, or do we need to appreciate the impact of different endotypes in a type 2 immune response at first sight, and thus, to combine different treatments to reach our goal in those patients?

NEW QUESTIONS TO ADDRESS

Although type 2 inflammation regularly dominates the scene in “eosinophilic” nasal polyps, neutrophils may be present also, driven either by IL-17 or by CLCs, as already specified. The relevance of this neutrophilic inflammatory part is unclear so far: will it just disappear with the biologic treatment directed toward type 2, specifically, if it is induced by CLCs, or will it persist or even expand, driven by IL-17, once the type 2 reaction has been suppressed? Is type 1 or type 3 inflammation causing failure in dominant type 2 inflammation and associated with nonresponse? Is only the purely non-type 2 neutrophilic polyp not responding to biologic treatment? Or is lack of response also seen in eosinophilic nasal polyps with especially severe inflammatory signatures? Are there different reactions in different patients and conditions? And finally, do we need to apply different targeted therapies in parallel to overcome the problem in some patients? Would it be advantageous to combine strategies directed toward IL-5 and IL-4/13, at least at the start of treatment, to obtain a faster, better, and broader response? Thus, with the complete understanding of endotyping in CRSwNP still remaining a challenge, can we already take the step to translation into daily practice? This dilemma is provoking a lot of questions to be answered; in simple words, a tissue eosinophil—or even less so a blood eosinophil—does not yet make a type 2 diagnosis with clear therapeutic consequences. Only large clinical trials with biologics, including solid research into mucosal tissue, nasal secretion, and blood biomarkers, will finally enable us to answer these questions.

Whereas for type 2 asthma, a preference concerning the antibody approach to be selected has been provided,²⁹ focusing primarily on the allergic aspect of severe asthma, and on blood eosinophils in patients with severe asthma thereafter, no such preference and care pathways have been elaborated for CRSwNP. The reason is that no parameter that would be associated with treatment response—not in the blood, serum, or nasal secretions or tissues—has been identified for any biologic yet. Patients with severe CRSwNP do show elevated levels of serum IgE and blood eosinophils and may or may not be allergic to inhalant allergens, and only then is there rationale to apply any of the aforementioned type 2 biologics; however, there are still no markers to predict response of an individual patient to any of the biologics that could be derived from the current studies. Thus, how do we decide on the order in which to try different biologics, and which to try first? In a situation, where only 1 biologic, dupilumab, is available for the indication CRSwNP, the question is easy to answer. However, we will likely have 4 or more biologics within a year or 2, and as for asthma, arguments may be pushed forward to direct the choice on the basis of eosinophils, allergy, or IgE. For the sake of patients and the community, arguments should instead focus on efficacy, responder rates, safety, and possibly costs of treatment.

Lacking biomarkers to predict the right drug for an individual patient with type 2 CRSwNP, the approach to “treat with the first choice and observe the response” seems the best we can do at the moment; however, in all studies performed with biologics so far, a third to nearly half of the patients did not respond sufficiently to the treatment, and evidence-based stopping rules have to be introduced in due time to identify nonresponders early after start of treatment as a compromise. Fortunately, unlike in patients with severe asthma, in whom exacerbations at longer time periods need to be observed and counted, the follow-up in patients with CRSwNP will be easier. First, there is the smell, which may come back within 4 to 8 weeks^{27,30} and may serve as a very strong sign of response to treatment; the patient will be very pleased to report this phenomenon to the physician! However, in patients who have had repeated surgical procedures and are older, smell cannot be regained and therefore cannot serve as a criterion. Second, nasal endoscopy is relatively easy to perform and standard among ear, nose, and throat specialists, and even if the nasal polyp score is not familiar to all colleagues, a screenshot of the nasal endoscopy can be taken easily before the start of treatment and compared with the situation 3 to 6 months later. And although many of us do not use visual analog scales or the Sino-nasal Outcomes Test (SNOT-22) on a regular basis in daily practice, the patient will happily report the changes observed. Smell testing and nasal polyp scoring easily deliver the objective measures to confirm treatment response. The nose really is easy to access for control.

CONCLUSIONS

For CRSwNP, endotyping thus makes a great difference in our clinical practice and provides the basis for progress in understanding and treating our patients better. At the same time, surgical techniques and skills and our understanding of immunology “in practice” need to be improved. Whereas clinical signs of CRS with or without polyps and its comorbidities allow phenotyping the patients with sinus disease, they may also be indicative for the endotypes of CRS; this allows us to predict the natural course of disease and to select adequate treatment

approaches—with increasing importance—from pharmacotherapy to surgery and finally to biologic agents (Fig 2). There does not need to be any discussion that the indication of a biologic drug such as dupilumab, omalizumab, benralizumab, or mepolizumab should be based strictly on type 2 indicators for any individual patient.³⁰ These indicators will need continuous adjustment on the basis of large databases to improve the selection of patients, not only specifically for biologics but also for adjusted surgical approaches. Endotyping in CRS will be with us for a long time, be the engine for progress in diagnosis and treatment, and likely increase the demand for specialized centers. Maybe this is the way for specialists in the upper and lower airways to work together even more closely.

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