

Endotype-driven care pathways in patients with chronic rhinosinusitis



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1. To understand the role of type 2 inflammation in patients with chronic rhinosinusitis.
2. To describe the use of biologics in the treatment of chronic rhinosinusitis.
3. To understand biomarkers involved in chronic sinus inflammation.

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Chronic rhinosinusitis (CRS) has been differentiated clinically into CRS without nasal polyps and CRS with nasal polyps, with both forms subjected to glucocorticosteroid and antibiotic treatments and, if not successful, to nasal and sinus surgery tailored to endoscopic and computed tomographic scan findings. The elaboration of endotypes based on pathomechanisms involving different immune responses offers new possibilities in terms of prediction of prognosis and risks and sophisticated guidance in personalized pharmacotherapy, surgical approaches, and innovative treatment approaches in the CRS field with various biologics. Surgical approaches can vary from classical functional

endoscopic sinus surgery to extended and “reboot” approaches, with the idea to completely remove the dysfunctional and inflamed mucosa and replace it with a newly grown healthy mucosa. Biologics in this field are targeting the type 2 cytokines IL-4, IL-5, and IL-13, as well as IgE. Phase I and II study results are promising, and phase III studies are currently being performed. The development of endotype-driven integrated care pathways appreciating these innovations are now needed for the management of CRS. (*J Allergy Clin Immunol* 2018;141:1543-51.)

Key words: Chronic rhinosinusitis, nasal polyps, pharmacotherapy, surgery, biologics, endotypes, type 2 inflammation, integrated care pathways

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Chronic rhinosinusitis (CRS) is defined as an inflammatory disease within the paranasal sinuses lasting for more than 12 weeks; patients often continue to experience symptoms for years and decades, with symptoms aggravating over time.¹ These symptoms can comprise nasal blockage, secretion and postnasal drip, headache and facial pain, and loss of smell and taste. CRS is considered frequent in the European Union and United States,^{2,3} having a great effect on patients' quality of life, as well as on health care spending. Guidelines for its management are available in the United States and European Union.

Abbreviations used

CRS: Chronic rhinosinusitis
 CRSsNP: Chronic rhinosinusitis without nasal polyps
 CRSwNP: Chronic rhinosinusitis with nasal polyps
 CT: Computed tomography
 ICP: Integrated care pathway
 ILC2: Type 2 innate lymphoid cell
 SE-IgE: *Staphylococcus aureus* enterotoxin-specific IgE

Traditionally, primary care physicians and specialists share the medical care for those patients, with the specialists focusing on more severe disease and eventually using surgical approaches and, where nasal polyps are involved, using nasal endoscopy for monitoring. Although pharmacotherapy for CRS, specifically nasal polyps, is available, disease control or even healing is unlikely, and surgery is often indicated. However, specifically in patients with nasal polyps, even the combination of surgery and pharmacotherapy might not be able to control the disease and its symptoms.^{4,5}

Biologics might offer relief for those patients in the future.^{6,7} However, to indicate the use of biologics in an individual patient will require more than interpretation of nasal endoscopies and computed tomographic (CT) scans of the sinuses. An understanding of the pathomechanisms responsible for the patient's unresponsiveness to currently available treatment, an understanding of the necessary selection of patients and the best choice of drug in an individual patient, and the likelihood of response to a specific biologic treatment will be based on a basic understanding of sinus inflammation, which is termed "endotyping of CRS," eventually also involving biomarkers. Thus specialists treating CRS will have to learn about inflammation and the patient's immunologic background to be able to handle this challenge.

CT scanning and nasal endoscopy will provide differentiation of chronic rhinosinusitis without nasal polyps (CRSsNP) and chronic rhinosinusitis with nasal polyps (CRSwNP) and allow the treating physician an appreciation of the extent of disease within the sinuses, but these methods will definitely not allow to make conclusions about the underlying inflammatory disease of the nasal and sinus mucosae. This currently results in a one-size-fits-all approach for pharmacotherapy and surgical principles, which is not the way forward in achieving the best outcomes.⁷ Furthermore, the causal principles of sinusitis, as discussed in the 1980s, such as narrow clefts causing limitations of drainage and ventilation and problems of mucociliary clearance and transport of secretions,^{8,9} have not integrated any thoughts on inflammation. The principles of functional endoscopic sinus surgery are also based on a very mechanical understanding of sinus pathology. The differentiation of inflammatory pathomechanisms and consequent endotyping of CRS were not introduced into disease management before 2012¹⁰ and have only recently been elaborated.¹¹ However, endotype-based therapy will be specifically necessary for severe and recurrent CRS and will be inevitable, especially with the availability of biologics in the near future.^{12,13}

CURRENT GUIDELINES IN THE EUROPEAN UNION AND UNITED STATES

The European Rhinologic Society¹ and the American Academy of Otolaryngology–Head and Neck Surgery¹⁴ have initiated the development of guidelines for the management of sinusitis/

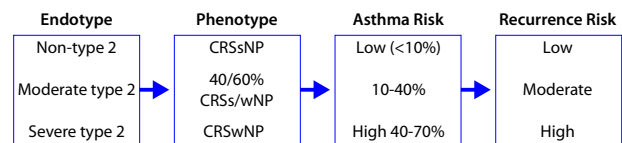


FIG 1. Endotypes of CRS and clinical consequences.

rhinosinusitis, including CRS. Neither document bases any recommendations on endotypes of CRS, although the European Position Paper on Sinusitis and Nasal Polyps guidelines mention endotypes under "Research needs and strategies." Thus neither recommendations for the use of pharmacotherapies, including antibiotics, corticosteroids, and other drugs, nor for indications for surgery and eventually differentiated approaches are endotype based in these documents. mAb studies are discussed briefly only in the European Position Paper on Sinusitis and Nasal Polyps. Furthermore, none of these guidelines formulate care pathways.

Integrated care pathways (ICPs) are structured multidisciplinary care plans detailing essential patient management steps. They promote the translation of guidelines into protocols and their subsequent application to clinical practice. Future documents should integrate the approach to endotyping CRS into management recommendations, also appreciating precision medicine in this field and the formulation of ICPs.

ENDOTYPES AND PATHOMECHANISMS

For more information on endotypes and pathomechanisms, see Fig 1. In 2012, a publication from our group mentioned that CRS phenotypes should be differentiated further into endotypes of CRS based on inflammatory patterns, including prominent cytokines, such as IL-5 and *Staphylococcus aureus* enterotoxin-specific IgEs (SE-IgEs).¹⁰ An important role for these endotypes could be deduced from their predictive value for asthma comorbidity¹⁵ and disease recurrence¹⁶ and the future need for allocation of a role for biologics, such as anti-IgE, anti-IL-5, and anti-IL-4 receptor α , in care pathways for CRS.⁶ This approach was further elaborated on in the PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology.¹²

A recent publication developed endotypes of CRS, building on unsupervised cluster analysis of tissue biomarkers that were consequently validated by relating them to clinical findings of importance, such as disease phenotypes and asthma comorbidity.¹³ The authors defined 3 endotypes, (1) non-type 2, (2) moderate type 2, and (3) severe type 2 immune reactions, based on significant upregulations of cytokines and mediators in diseased versus healthy subjects or patients with severe versus moderate disease (Fig 1). Whereas the non-type 2 group mostly had CRSsNP with little asthma comorbidity, the moderate type 2 inflammatory pattern indicated CRSwNP with increased asthma prevalence. Severe type 2 inflammation was associated with CRSwNP in nearly all cases and asthma comorbidity in up to 70%. This latter endotype was also characterized by higher concentrations of tissue IgE and expression of SE-IgEs. Recently, serum biomarkers were proposed, allowing the differentiation of non-type 2 and type 2 CRSwNP endotypes and also indicating moderate versus severe type 2 inflammation.^{17,18}

In the literature 4 distinct but overlapping classification schemes have emerged to define endotypes within the CRSwNP phenotype and have recently been summarized as follows: (1) a

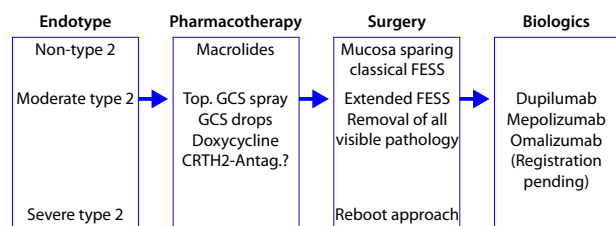


FIG 2. Therapeutic approaches according to endotypes. *CRTH2*, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *FESS*, functional endoscopic sinus surgery; *GCS*, glucocorticosteroids.

type 2 cytokine-based approach, (2) an eosinophil-based approach, (3) an IgE-based approach, and (4) a cysteinyl leukotriene-based approach.¹⁹ Many more approaches are possible and can be developed. However, differentiation based on type 2 cytokines and their downstream products is most meaningful for currently developed biologics, including anti-IL-5, anti-IL-4, anti-IL-13, or anti-IgE, and therefore is preferred. IL-33 and thymic stromal lymphopoietin also produced by epithelial cells in patients with CRSwNP and are potential therapeutic targets for this disease for which biologic therapy is being considered.⁶

Other cytokines, such as IL-17, interferons, TNF- α , and IL-22, are also expressed in patients with CRSsNP/CRSwNP and can be associated with specific bacterial stimuli^{11,20} but have not shown clear associations with comorbidities or clinical outcomes. Studies demonstrating a beneficial effect of their antagonism are also currently lacking, and studies in asthmatic patients with anti-TNF and anti-IL-17 have not shown benefits either. It is unclear whether these cytokines play a role in patients expressing a type 2 immune reaction combined with other type 1-related cytokines that do not adequately respond to anti-type 2 cytokine therapies.

The clinical associations mentioned above can allow conclusions on endotype without the use of biomarkers in many cases. A patient with CRSwNP with comorbid late-onset asthma and/or former surgeries with disease recurrence likely expresses type 2 inflammation.^{15,16} However, the predictive value of these associations has not been tested rigorously, and a differentiation between moderate and severe type 2 inflammation might not be possible. Early acquired allergic sensitizations to inhalant allergens do not seem to affect inflammation in the tissue or expression of T_H cells in the peripheral blood of patients with CRSwNP.^{21,22}

Type 2 inflammation in patients with CRS involves the T_H2 cells and, as recently discovered and extensively described, also the epithelial cell-activated type 2 innate lymphoid cells (ILC2s), joining innate and adaptive immunity patterns to release type 2 cytokines, including IL-4, IL-5, and IL-13.^{23,24} Epithelial cell-derived signals activate ILC2s and later T cells, although the contributions of these cell populations have not been clarified sufficiently. Both ILC2s and T cells release a similar pattern of type 2 cytokines, which then have a negative effect on many factors detrimental to sinus disease, including (1) integrity of the epithelial barrier²⁵; (2) hyperplasia of mucosal glands and mucus production²⁶; (3) development of functional macrophages to phagocytose bacteria²⁷; (4) the possibility to release interferons on encounter with viruses²⁸; (5) development of T follicular helper cells and formation of immunoglobulins, with increased IgE production²⁹; (6) activation of the complement system³⁰; (7)

recruitment and activation of mast cells and eosinophils with the release of eosinophil extracellular traps³¹; and, last but not least, (8) typical remodeling of the mucosa with fibrin deposition.³²

Possibly because of these mucosal deficits, *Staphylococcus aureus* is a frequent colonizer of polyps and also resides intramucosally. Proteins of *S aureus* have been identified within polyp tissue,³³ and recently, *S aureus* has been demonstrated to regulate IL-5 release.³⁴ Among those proteins are classical staphylococcal enterotoxins that are also called superantigens, but also serine protease-like proteins³⁵ have been identified as superallergens, further shifting the immune reaction to type 2 through release of IL-33.³⁶ *S aureus* also attracts eosinophils to migrate to the epithelium and release eosinophilic extracellular traps, further destructing the airway epithelium and thus contributing to persistence of disease.³¹ IgE antibodies to *S aureus* enterotoxins are regularly associated with increased mucosal IgE and IL-5 concentrations and more severe clinical disease.¹¹ These changes can lead not only to local mucosal inflammation within the sinuses but also can involve the lower airways (comorbid asthma) and can result in disease persistence³⁷ and recurrence of disease after surgery¹⁶; they definitely impair the mucosal defense against bacterial and viral infections. Such changes are a function of the severity of type 2 inflammation, which is typical for type 2 inflammation and different from non-type 2 immune reaction patterns.³⁸ It also might be assumed that a correction of the deviated type 2 immune reaction (eg, by biologics) will correct the deficits in epithelial integrity, bacterial and viral defense.

PRINCIPLES OF THERAPY BASED ON ENDOTYPES

For more information on principles of therapy based on endotypes, see Fig 2. The extension of CRS disease at the CT scan or nasal endoscopy level and the degree of symptomatology of the patient should indicate the need for intervention. The endotype of CRS in an individual patient should guide the intervention decision on the specific treatment to be applied from the choice of pharmacotherapy, surgical approach, or possible indication of biologics in the future (Fig 2).¹¹ This approach will optimize the effect of treatment in the individual patient (personalized medicine), optimize the use of resources, avoid the need for recurrent interventions, reduce the risk for disease progression, and help identify the need for maximal treatment possibly organized in specialized centers.

These endotypes are valid internationally and allow comparisons between patient groups and populations all over the world.^{39,40}

THE CHOICE OF PHARMACOTHERAPY

According to current guidelines, topical glucocorticosteroids, short-term oral glucocorticosteroids, and long-term antibiotics, including macrolides and doxycycline, are to be considered for the treatment of CRS.^{1,14} However, glucocorticosteroids do target type 2 inflammatory responses better than non-type 2 responses,⁴¹ and glucocorticosteroid resistance has been observed even in patients with type 2 CRSwNP.³⁷ Thus the use of glucocorticosteroids might not be efficacious in many patients with CRS in both phenotypes, with and without nasal polyps. Endotyping can allow for identification of groups of patients with CRS with a high

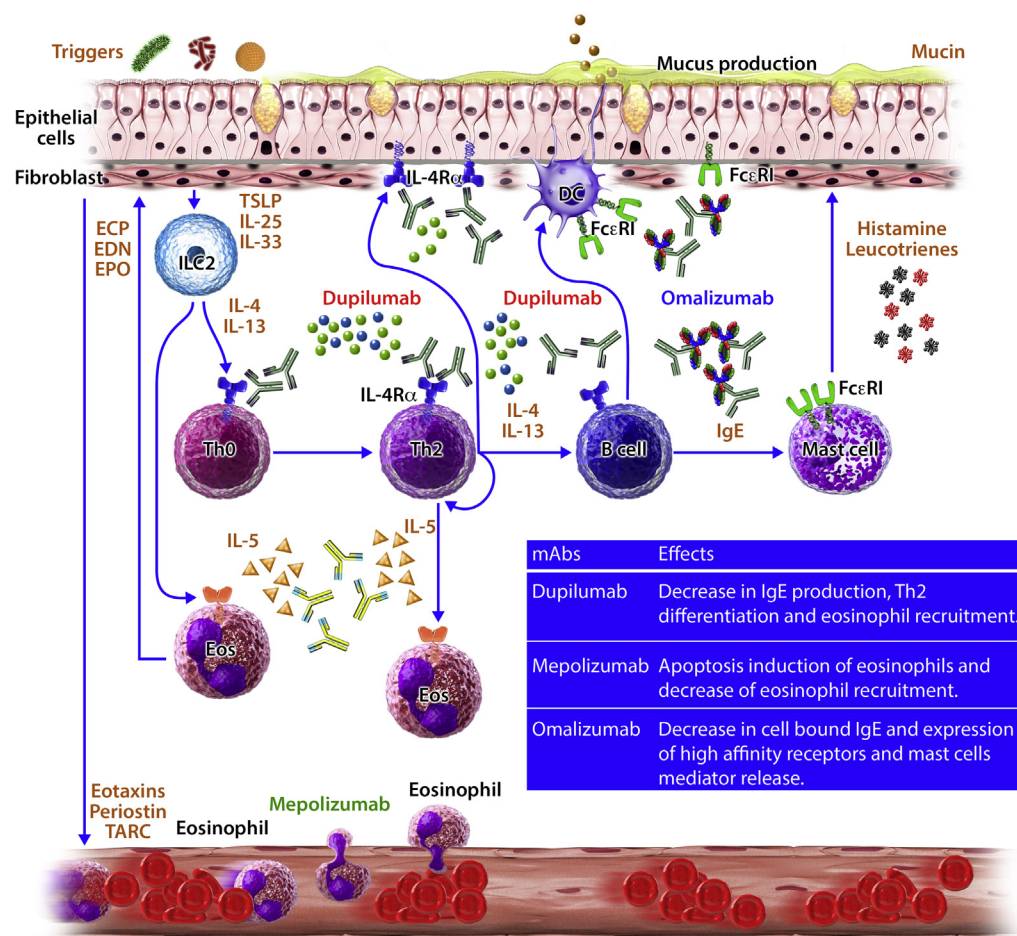


FIG 3. Mechanisms of action of biologics in patients with CRSwNP. DC, Dendritic cell; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; Eos, eosinophils; EPO, eosinophil peroxidase; IL-4R α , IL-4 receptor α ; TSLP, thymic stromal lymphopoietin.

likelihood of success, such as patients with a moderate type 2 immune reaction.

Furthermore, there is evidence that low-dose long-term macrolides will be successful in patients with neutrophilic rather than eosinophilic inflammation, as was shown in asthmatic patients.^{42,43} In contrast, long-term doxycycline treatment has been used in patients with type 2 inflammatory nasal polyps.¹ Antagonists of oral prostaglandin D₂/chemoattractant receptor-homologous molecule expressed on T_H2 cells also can target type 2 rather than non-type 2 immune reactions in patients with CRS.⁴⁴

SURGICAL APPROACHES: MUCOSA SPARING OR REBOOT?

In patients with CRSsNP, disease recurrence after adequate sinus surgery is infrequent, whereas in patients with CRSwNP, the percentage of patients with disease recurrence after surgery is considered high, with figures ranging as high as 38% to 60% at 12 months of follow-up.^{4,45} Causes for treatment failure and disease recurrence have been studied, and factors such as bronchial asthma, eosinophilia, aspirin-exacerbated respiratory disease, and atopy were found to be the most important clinical risk factors, all pointing to a type 2 inflammation endotype.^{46,47} Therefore patients with recurrent and difficult-to-treat CRS are often exposed repeatedly to surgical management of various kinds, and in a

recent European study involving 800 patients, more than 20% of those undergoing any surgery for CRS reported 4 or more prior surgeries, with some patients undergoing 30 or more surgeries in their lifetimes (unpublished data). The spectrum of surgical options ranges from simple polypectomy with a snare or forceps, which is a minimally invasive sinus surgery technique, to more extended “radical” procedures.⁴⁷ Endoscopic sinus surgery has been the gold standard surgical approach to sinonasal diseases over the past 2 decades in the United States and European Union, especially after the pioneering studies of Messerklinger in which he demonstrated that each sinus has a predetermined mucociliary clearance pattern draining toward its natural ostium; these observations supported mucosa-sparing surgery.^{8,9} However, although these considerations might be relevant to CRSsNP, they were shown to be often unsuccessful in patients with CRSwNP, and they certainly do not consider inflammatory endotypes.

Because there are deficits at multiple mucosal levels (see above) and an immunologic memory (memory T cells) maintaining the existing immune deviation in the presence of persistent stimuli, such as bacteria, the probability of restoring a normal mucosa with remaining diseased mucosa in the sinuses might be low. Therefore recurrences after sinus surgery might be a question of failed completeness of mucosal removal. In contrast, removal of the type 2 inflammatory environment might allow undisturbed re-epithelialization of the sinus walls. Extensive endoscopic sinus

TABLE I. What to expect from biologics in the treatment of CRSwNP?

Clinically	
Reduction of endoscopic nasal polyp score	D, M, O
Lund-Mackay CT scan score	D, O
Reduction of relevant nasal symptoms	D, M, O
Increase in smell (UPSIT and VAS)	D, M, O
Increase in quality of life (SNOT-22 and RSOM-31)	D, M, O
In asthmatic patients	
Increase in lung function (FEV ₁ percent predicted)	D, O
Asthma control (ACQ and AQLQ)	D, O
Biomarker	
Reduction in blood eosinophil numbers	M
Reduction in serum IgE levels	D, O
Reduction in tissue eosinophil numbers	D, M

ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; D, dupilumab; M, mepolizumab; O, omalizumab; RSOM-31, Rhinosinusitis Outcome Measure; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.

surgery approaches, such as the “nasalization” reported by Jankowski et al⁴⁷ or modified Lothrop procedures, have been used intuitively by some surgeons; recurrence rates were reportedly lower in case series, and rates of major complications did not differ significantly between the extensive and less invasive surgical techniques.⁴⁸

However, these approaches were not based on endotyping nor did they target the inflammatory mucosa and related deficits. A recently proposed “reboot approach” does fill this gap, focusing on removal of the inflamed mucosa from all sinuses. Preliminary data from a study following up 50 patients who underwent surgery for CRSwNP at Ghent University Hospital using different operative techniques showed that the reboot approach resulted in significantly fewer recurrences (defined as new growth of at least small polyps within 2 years after surgery) than the mucosa-sparing classical sinus surgery approach (45% vs 13%, $P < .001$). All patients showed a type 2 inflammatory pattern, with comparable concentrations of type 2 cytokines in tissue; 60% of the subjects had previous surgery; and 62% had comorbid asthma (S. Alsharif, C. Bachert, et al, unpublished). It is obvious that this “reboot” approach should only be considered in a specific group of patients with severe type 2 CRSwNP.

Also, the timing of surgery can be reconsidered; earlier surgery after diagnosis was beneficial to patients in terms of surgical results and asthma onset compared with prolongation of pharmacologic treatment and later (>5 years) surgery.^{49,50} This observation underlines the need to focus on the long-term efficacy of surgery but also other treatment approaches in comparison with surgery, aiming to control disease and increase health-related quality of life of the patients for several years or even decades rather than months. There is need to also include the specific risks of disease, such as recurrence and asthma comorbidity, in evaluation of treatment approaches.

MECHANISMS OF ACTION OF TYPE 2 BIOLOGICS

For more information on mechanisms of action of type 2 biologics, see Fig 3. Treatment options for nasal polyps are comparable with those for severe asthma, targeting the type 2 endotype, which is characterized by a prominent role of cytokines, such as IL-4, IL-5, and IL-13, and IgE.⁵¹ However, the mechanisms of

TABLE II. Patient stratification for type 2 immune response

Biomarkers (larger clinical studies can modify the proposal)

- Blood eosinophil count >300/ μ L
- Total serum IgE level >150 kU/L
- Presence of serum SE-IgE
- Increased serum periostin level
- Lower airway biomarkers

Clinical

- Presence of comorbid late-onset asthma
- Recurrence after adequate sinus surgery

action of these biologics have not been clarified completely. Although mepolizumab and benralizumab primarily target activation and survival of eosinophils in tissue and peripheral blood,^{52,53} omalizumab targets free total serum IgE,⁵⁴ and dupilumab acts as a broad anti-type 2 antagonist interfering with IgE and chemokine production.⁵⁵ This effect obviously also leads to a reduction in numbers of mucosal tissue eosinophils as a secondary phenomenon (K. Jonstam, personal communication). However, biologics have additional effects on biomarkers, such as levels of periostin, eosinophilic cationic protein, and chemokines and serum and nasal secretion of IL-5, either locally or systemically and therefore might also have a broader anti-type 2 spectrum of activities than anticipated.⁵⁶ Biologics can have further effects on the course of disease, as has been demonstrated for omalizumab in asthmatic patients; although escalating the dose of glucocorticosteroids does not reduce virus-induced wheeze, omalizumab reduced viral exacerbations in inner-city asthmatic children.^{57,58} This might be related to an improved IFN- α response to rhinovirus,⁵⁹ suggesting that type 2 inflammation causes increased susceptibility to viral illness.²⁸ Bacterial infections and colonization can be reduced similarly by reinstallation of the epithelial barrier and normalization of macrophage function.

Neither the optimal targets for biologics (eosinophils and IgE) nor the criteria to select patient groups or predict response to treatment in an individual patient (eg, allergy and blood eosinophil counts) have been clearly defined in patients with CRS. The use of existing biomarkers has not been helpful to predict therapy outcome in either the short or long term, although it is obvious that patients receiving any of these antibodies should experience type 2 immune reactions.

WHAT TO EXPECT FROM BIOLOGIC TREATMENT

For more information on what to expect from biologic treatment, see Table I. From the currently available phase 1 and 2 studies performed in patients with CRSwNP, biologics in general can decrease the nasal polyp score by about 2 points (baseline, 5–6 points) on average after 24 weeks of treatment,^{52,54,55} corresponding to the maximal effect of a short course of oral glucocorticosteroid treatment.⁶⁰ Unlike glucocorticosteroids, however, biologics are able to maintain this effect for several months or years when continuously applied without additional adverse events, whereas long-term application of oral glucocorticosteroids should be considered very restricted because of adverse events.⁶¹

With reduction of the nasal polyp score, the typical symptoms of CRSwNP, such as nasal obstruction, secretion, and postnasal drip, as well as loss of smell, might significantly decrease, and

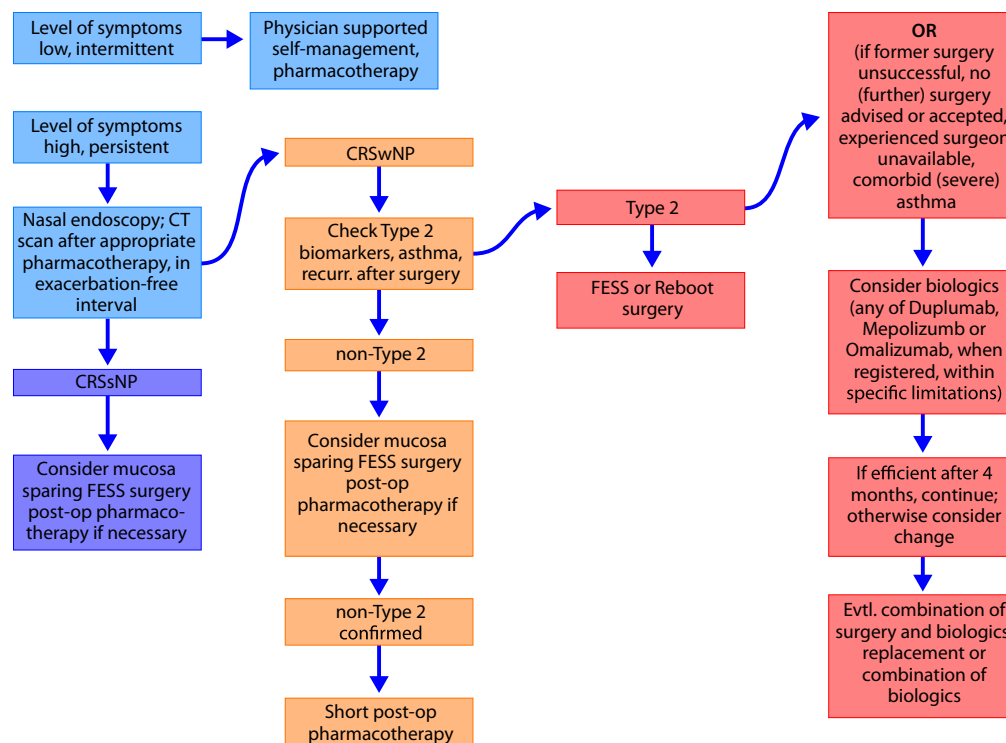


FIG 4. ICPs for CRS (regional differences and new studies can lead to changes of the ICP). FESS, Functional endoscopic sinus surgery.

specific and general measures of quality of life significantly increase. Changes in polyp volume can be objectivized by using a CT scan, the University of Pennsylvania Smell Identification Test, and peak nasal inspiratory flow measurements for nasal obstruction. Furthermore, as has been evaluated recently, the need for surgery can decrease significantly,⁵² although there is no common definition of such need. Thus the reduction of need for surgery remains arbitrary to quantify; it depends very much on definitions, and this difficulty is common to all currently studied biologics.

In patients with comorbid asthma, scores on asthma-specific quality-of-life and control tests significantly improve, and although not shown for all drugs, lung function parameters (FEV₁ percent predicted) can improve as well.⁵⁵

Depending on the specific biologics, levels of specific biomarkers will decrease; however, these biomarkers are treatment specific and cannot be generalized. Thus, to monitor a specific biologic, the biomarkers have to be selected appropriately; for example, blood eosinophil numbers can be suitable to monitor the application of mepolizumab but not dupilumab, which did not show any suppression of blood eosinophil counts.⁵⁵ Frequent adverse events include nasopharyngitis, headache, and injection-site reactions, but severe drug-related adverse events are rare.

The coming phase 3 study results for dupilumab, mepolizumab, benralizumab, and omalizumab will certainly increase our knowledge on the efficacy and adverse events of biologics for CRSwNP and might allow better positioning of drugs in comparison with each other. Here, not only the maximal and average short-term effects but also the long-term effects, responder rates, application route and frequency, and finally costs of treatment have to be considered.

PATIENT STRATIFICATION FOR BIOLOGICS

For more information on patient stratification for biologics, see Table II. Different from severe asthma, no registration for any of these drugs has been achieved for the indication of nasal polypsis; phase 3 studies with mepolizumab (anti-IL-5), omalizumab (anti-IgE), dupilumab (anti-IL-4 receptor α , covering both the IL-4 and IL-13 pathways), and benralizumab (anti-IL-5 receptor α) are currently being performed or in preparation. Furthermore, limitations for use could be implied by health authorities. Therefore advice on the stratification of patients should be updated regularly.

It is mandatory to verify that the patient has type 2 CRSwNP. This can be achieved based on biomarkers, such as blood eosinophil counts or total serum IgE levels, but also based on clinical signs, such as late-onset asthma comorbidity or recurrence of disease after appropriate surgery (Table II); other biomarkers, such as periostin and SE-IgE levels, might assist in the near future.¹⁷ However, no further advice on patient selection on the basis of biomarker values can be provided. In all studies with mAbs in patients with CRSwNP performed thus far, blood eosinophil counts and total serum IgE levels were increased to greater than normal values at the start of treatment but did not qualify to predict individual responses to treatment. Therefore blood eosinophil counts, serum IgE values, and atopic status are not suitable for specific drug selection.

Biologics are expensive treatments that should only be continued when efficacious. Therefore it is important to assess whether they should be continued after an appropriately short course of treatment.⁶² The decision to continue treatment can be based on a reduction of symptoms, the lack of troublesome adverse

events, and also a reduction in polyp score by at least 1 point (Davos score of 0–4 per side, 8 in total; see Bachert et al⁵⁵) within 4 months of treatment. A reduction of 2 points is indicative of a good clinical response at that time point and clearly differentiates the effect from the effect of topical glucocorticosteroids. The same period has also been proposed for omalizumab in severe asthma treatment based on several controlled and real-life studies.⁶³ Furthermore, the appropriateness of continuous treatment should be checked regularly thereafter (eg, every year). Because studies with biologics in proof-of-concept studies have thus far been limited to 16 weeks of medication, no information is currently available on the reduction in polyp volume and symptoms over time, the time to reach a plateau or eventually full remission, and the necessary dosing schemes to maintain optimal effects. The current phase III studies will likely shed more light on these questions and will guide recommendations on stopping rules.

TRANSLATION INTO DAILY PRACTICE: ICPs

For more information on translation into daily practice, see Fig 4. ICPs are structured multidisciplinary care plans detailing key steps of patient care. They promote the translation of guidelines into local protocols and their subsequent application to clinical practice. ICPs differ from clinical practice guidelines because they are used by a multidisciplinary team and focus on the quality and coordination of care. ICPs for airways diseases have been proposed⁶⁴ and implemented in patients with allergic rhinitis by using mobile technology.⁶⁵

In patients with CRS, several steps should be considered. Many patients are underdiagnosed and self-managed. It is important to propose a better recognition of the disease, in particular at the family physician and pharmacy level, because patients can use over-the-counter medications, including long-term decongestants. In primary care antibiotics and oral or depot injection glucocorticosteroids are still often used, and it is important to inform physicians of the need for a specialist advice.

The severity of symptoms is decisive for the need and choice of any treatment; recently, the MySinusitisCoach app has been introduced to monitor symptoms in patients with CRS.⁶⁶ This app can be used to monitor symptom severity and response to treatment and supports the self-management of patients with mild symptoms. It is based on the Mobile Airways Sentinel Network,⁶⁵ which can follow the control and medications of patients with allergic rhinitis. Moreover, it provides objective information for adherence to treatment and helps the specialist to decide earlier whether a surgical procedure is needed.

At the specialist care level, a stepwise approach can be considered. The differentiation of patients with CRSsNP and CRSwNP based on nasal endoscopy and clinical criteria is still appropriate; CT scanning is indicated when surgery is planned or other diagnoses need to be excluded. Questions regarding smoking status and comorbidities should be asked, and allergy testing should be performed to be informed about factors possibly affecting treatment.

No endotyping approaches of clinical relevance have been described for patients with CRSsNP thus far. Although about half of the patients with CRSsNP also demonstrate mild-to-moderate type 2 inflammation in the sinus mucosa, the relevance of this inflammation is currently unclear.

In patients with CRSwNP, blood eosinophil counts and total serum IgE levels can be measured to differentiate type 2 from non-type 2 inflammation; further biomarkers, such as periostin and SE-IgEs have been proposed but need to be validated according to proposed criteria⁶⁷ in larger cohorts. This information, together with disease severity, can be used for decisions on disease management, such as type of surgical approach and consideration of use of biologics. Apart from the current symptoms, risk prevention (comorbid asthma and disease recurrence) should be taken into consideration for such decisions.

The surgical approach should be tailored according to the endotype, from “functional mucosa-sparing endoscopic sinus surgery” for symptomatic but uncomplicated CRSsNP and non-type 2 CRSwNP to the “reboot” concept with complete removal of the inflamed and defective sinus mucosa for moderate-to-severe type 2 inflammation.

Biologics are possibly a choice in the near future for patients with type 2 CRSwNP when classical treatment approaches do not provide symptom control. Patients with severe asthma and nasal polyps can receive biologics for their asthma, also controlling sinus disease. Further studies are needed to estimate the potential for a reduction in disease risk by early use of biologics. Currently, there are no data examining combination therapy with different biologics for those who are partial responders or nonresponders to any of the mAbs.

Once registration of a biologic for CRSwNP has been achieved, specifically for the decision for surgery or treatment with biologics, the patient should be fully informed about short- and long-term expectations, effects, adverse events, and complications and share in the decision making.

SUMMARY

With the impressive increase in knowledge about immune pathomechanisms of CRS and the expectation of the first biologic registered for the treatment of severe/recurrent nasal polyposis and being available within 2 years, the urgent need for endotyping individual patients and the development of endotype-based care pathways for patients with CRS is evident. Similar to the asthma terminology, we can at least differentiate type 2 from non-type 2 immune reactions and recognize the clear association of type 2 disease with more severe clinical disease expression, recurrence, and asthma comorbidity. Thus endotyping becomes specifically relevant in the more severe patient group, and biologics targeting type 2 inflammation in severe asthma will also be available for the treatment of CRSwNP. We will learn from the current phase 3 asthma trials but need to appreciate the differences of asthma and nasal polyp disease in terms of outcome measures (reduction of exacerbations vs reduction of polyp volume), the dynamic of response to treatment, and the selection of biologics.

Although type 2 inflammation needs to be verified, no markers are available at present to select a specific biologic for an individual patient. This leads to the necessity of clinical monitoring after short-term and regularly after long-term use of biologics to avoid ineffective treatment and associated costs. Also for sinus surgery of severe CRSwNP, new techniques need to be developed to reduce short-term and possibly long-term risks, such as recurrence of disease and asthma comorbidity; an endotype-based approach is also necessary to tailor surgery to the needs of the patient and improve its outcome.

What do we know?

- CRSsNP mostly resembles a non-type 2 immune response (approximately 70% in Europe).
- CRSwNP mostly resembles a type 2 immune response (approximately 85% in Europe).
- CRSsNP shows significantly better long-term outcome after surgery than CRSwNP.
- Surgery in patients with severe CRSwNP is characterized specifically by recurrence.
- CRSwNP shows a high risk of late-onset comorbid asthma.
- Asthma in patients with CRSsNP is mostly of the early-onset and allergic variety.
- Biologics targeting type 2 immune markers might be efficient in patients with type 2 CRSwNP.

What is still unknown?

- What are the role and clinical significance of the (moderate) type 2 immune response in patients with CRSsNP?
- What are the biomarkers of high predictive value in patients with type 2 CRSwNP?
- What kind of surgical approach is best in type 2 versus non-type 2 CRSwNP?
- Which biologic should be used in which patient? What biomarkers predict response to individual drugs?
- When is the maximal effect reached with biologics (phase 3 studies pending)?
- What is the duration of biologic treatment and long-term dosing?
- Can biologics prevent asthma onset in patients with CRSwNP?
- What are the long-term sequelae of repeated systemic glucocorticosteroids in patients with CRSwNP?
- Once registered, what will be the restrictions from health authorities for biologics in patients with CRSwNP?
- ICPs need to be elaborated and adapted continuously.

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