Biologics for chronic rhinosinusitis with nasal polyps

Claus Bachert, MD, PhD,[a,b,c] Nan Zhang, MD, PhD,[a,b] Carlo Cavaliere, MD,[d] Wen Weiping, MD,[a] Elien Gevaert, PhD,[b] and Olga Krysko, PhD[b] *Guangzhou, China, Ghent, Belgium, Stockholm, Sweden, and Rome, Italy*

With the increasing recognition of the role of type 2 immune responses in chronic rhinosinusitis, its severity, recurrence, and comorbidities, several biologics targeting IL-4, IL-5, and IL-13 as well as IgE have been administered in small proof-of-concept studies. Recently, the first phase 3 trials have been reported with dupilumab, an IL-4 receptor antagonist, demonstrating a significant and clinically relevant reduction of the disease burden from polyp size and sinus involvement to symptoms and smell; these changes consecutively led to an important increase in quality of life. Finally, the biologic versus placebo treatment reduced the need for systemic glucocorticosteroids and sinus surgery significantly and clinically meaningfully. Dupilumab today is registered for the treatment of chronic rhinosinusitis with nasal polyps in Europe and the United States. Within a year, 2 further phase 3 trials with omalizumab and mepolizumab will be reported. With this development, without any doubt, a new era for the treatment of severe uncontrolled chronic rhinosinusitis with nasal polyps has begun. Questions on the indication of the biologics, the selection of patients, and finally criteria for monitoring the efficacy in individual patients need to be urgently answered, and care pathways need to be established integrating the current standard of care including surgery. (J Allergy Clin Immunol 2020;145:725-39.)

Key words: *Chronic rhinosinusitis, nasal polyps, endotypes, type 2 inflammation, biologics*

Abbreviations used

AERD:	Aspirin-exacerbated respiratory disease
CRS:	Chronic rhinosinusitis
CRSsNP:	Chronic rhinosinusitis without nasal polyps
CRSwNP:	Chronic rhinosinusitis with nasal polyps
CT:	Computed tomography
DBPCR:	Double-blind placebo-controlled, randomized
EC:	Epithelial cell
ECP:	Eosinophil cationic protein
GCS:	Glucocorticosteroid
IL-5Rα:	IL-5 receptor alpha
ILC2:	Type 2 innate lymphocyte
NPS:	Nasal polyp score
PoC:	Proof-of-concept
QOL:	Quality of life
SNOT-22:	22-item Sino-Nasal Outcome Test
TSLP:	Thymic stromal lymphopoietin
VAS:	Visual analogue scale

Chronic rhinosinusitis (CRS) without nasal polyps (CRSsNP) or chronic rhinosinusitis with nasal polyps (CRSwNP), together affecting more than 10% of the western population, can be diagnosed and differentiated by clinical symptoms and nasal endoscopy. CRS has long been managed by topical and eventually systemic glucocorticosteroids (GCSs) and sinus surgery, if steroids were unsuccessful.[1-3] Furthermore, there are clinical traits of CRS, such as CRS with asthma, mostly noninvasive fungal disease, CRS in cystic fibrosis, CRS with aspirin-exacerbated respiratory disease (AERD), and other subgroups. However, only recently it became evident that these clinical subgroups may be driven by similar pathomechanisms, and vice versa, similar clinical disease may have totally different background pathologies.[4,5] Trying to understand differences in the natural course of disease and response to treatment, we need to dive deeper and understand critical immune mechanisms, which are shared by some of these clinical traits, to increase our ability to predict the course of disease and response to treatment.[5] This led to the realization of the fact that specifically type 2 immune reactions—over all clinical phenotypes of disease, but representing about 80% of CRSwNP cases—tend to be more severe, recurrent, and accompanied by comorbidities. The differentiation of CRS into type 2 or non–type 2 disease has already improved our management of CRSwNP by selecting adequate surgical procedures and pharmacotherapy, and lately, with the advent of biologics, with innovative treatment options, here summarized as biologics.[6] With the first small successful clinical trial performed in 2006 in CRSwNP, following the progression in severe asthma, the last 14 years have seen a step-by-step, but pertinent progress also for CRSwNP, with several biologics studied in international multicenter phase 3 trials now. Dupilumab now already is registered for CRSwNP

From [a]the First Affiliated Hospital, Sun Yat-sen University, International Airway Research Center, Guangzhou; [b]the Upper Airways Research Laboratory and Department of Oto-Rhino-Laryngology, Ghent University, Ghent; [c]the Division of ENT Diseases, CLINTEC, Karolinska Institute, University of Stockholm, Stockholm; and [d]the Department of Oral and Maxillofacial Sciences, Sapienza University of Rome, Rome.

Disclosure of potential conflict of interest: C. Bachert acted as speaker and member of advisory boards for Sanofi-Aventis, Novartis, Glaxo, Astra-Zeneca, Stallergenes, ALK, Asit Biotech, Mylan, and Allakos. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication January 16, 2020; revised January 21, 2020; accepted for publication January 22, 2020.

Corresponding author: Claus Bachert, MD, PhD, First Affiliated Hospital, Sun Yat-sen University, International Airway Research Center, 58 Zhong Shan Er Lu, 510080 Guangzhou, China. E-mail: claus.bachert@ugent.be.

0091-6749/$36.00

https://doi.org/10.1016/j.jaci.2020.01.020

in the United States and Europe, and very recently, already several thousand subjects with CRSwNP in the United States received this biologic instead or combined with surgery and/or systemic GCSs. Within 1 to 2 years, we will have several antibodies available, all targeting type 2 immune reactions, to choose from for selected patients. ENT specialists, pulmonologists, and allergists need to master the innovative drugs, the selection of patients—and soon of biologics, the expected effects and side effects, as well as ways to monitor the patient's individual response to the biologic and correct the management accordingly. This review will describe the relevant pathophysiology, treatment targets, and corresponding biologic drugs as well as available studies in CRSwNP.

TYPE 2 INFLAMMATION IN CRSwNP

Eosinophils have been identified early in nasal polyps,[7] and their products such as eosinophil cationic protein (ECP) have already been measured nearly 50 years ago.[8] The cells stood in the focus of research in the 1980s, and Mygind et al[9] later summarized the knowledge as "Nasal polyps are eosinophilic, and corticosteroids can shrink them." Also, IgE was measured early in nasal polyps, just after the description of the—at that time—new immunoglobulin class.[10] Thus, components of type 2 immune reactions in nasal polyps have been identified long ago; the recognition of T-cell subsets,[11] however, and the recognition of the type 2 endotype, also appreciating the role of type 2 innate lymphocytes (ILC2s),[12] came later for the nose and sinuses.[4] Finally, the endotyping of CRS on the basis of a cluster analysis provided the link with clinical traits such as asthma and recurrence of disease after surgery for CRSwNP.[5] Although there are subjects with CRSsNP with increased markers of type 2 immune reactions,[5] these patients have not been identified as problematic in the management or treated with biologics yet.

The type 2 immune response is characterized by a marked infiltration of eosinophils and mast cells, goblet hyperplasia, and increased levels of ECP, eotaxins, total IgE, IL-5, IL-4, and IL-13.[13-15] Although sinonasal epithelial cells (ECs) serve as a first line of defense in the nasal cavities, they express multiple pattern recognition receptors to sense and react to proteolytic allergens, harmful invaders, and tissue damage. As such, ECs play an active role in the initiation and regulation of both innate and adaptive immune responses and can trigger a type 2–mediated response. In nasal polyps, ECs or EC subsets (eg, solitary chemosensory cells)[16] can produce IL-1, IL-33, thymic stromal lymphopoietin (TSLP), and/or IL-25 in response to various damage-associated molecular patterns (eg, ATP and high mobility group box 1),[17] pathogenic organisms (eg, *Staphylococcus aureus* and fungi),[18] and their related products (microbial DNA, toxins) or allergens.[17,19-21] The production of TSLP and IL-33 subsequently leads to the activation and accumulation of ILC2s, with the production of IL-5 and IL-13 as a result.[20,22,23] A recent publication from our group pointed to the importance of the CD117 and IL1RI double-positive ILC2 subset in the further orchestration of T_H2 response and eosinophil recruitment in nasal polyp mucosa.[12] In parallel and assisted by other cytokines, TSLP programs dendritic cells for mediating a T_H2-mediated response in a ligand for CD134 (OX40L)-dependent manner.[24] In addition, TSLP potentially synergizes with IL-1 and IL-33 to activate mast cells to produce type 2 cytokines.[25] Altogether, the epithelial-derived cytokines boost ILC2s, basophils, and mast cells, and orchestrate a T_H2-mediated immune response, leading to the production and secretion of IL-4, IL-5, and IL-13 in the mucosa. In turn, IL-4 and IL-13 can act directly on the ECs, causing decreased tight junction expression, enhancing mucus production, and sustaining a positive feedback loop.[26,27] In parallel with the expansion of T_H2 cells in CRSwNP, an expansion of B cells and plasma cells takes place.[13,28] Local activation, proliferation, class-switch recombination, and production of antibodies is thought to take place in B-cell clusters and follicle-like structures within the polyp.[29,30] IL-13 is known to drive IgE class switching in B cells, leading to an elevated local production of IgE, a well-known feature of nasal polyps.[13,29,31,32] The polyclonal IgE was found to be functional and able to activate mast cells in nasal polyps, in turn leading to type 2 cytokine production, eosinophil recruitment, and activation.[33,34]

The production of IL-13 further leads to expression of endothelial vascular cell adhesion protein 1 and other adhesion molecules, enabling the recruitment of lymphocytes, eosinophils, and basophils.[35] At the same time, IL-13 is able to drive the differentiation of recruited monocytes to alternatively activated (M2) macrophages, a phenotype that is known to accumulate in polyps and to show reduced phagocytosis.[36] Also, IL-13 induces the release of C-C motif chemokine receptor 3–specific chemokines by the epithelium. As such, the release of C-C motif chemokine ligand 13 (aka monocyte chemoattractant protein 4) and eotaxins-1, 2, and 3 result in the recruitment of eosinophils, mast cells, and basophils into the mucosa.[37] There, the presence of IL-5 promotes eosinophil survival and activation. As a consequence of the extensive activation, delayed apoptosis, and the presence of other triggers, eosinophils undergo extracellular DNA trap cell death (EETosis) at epithelial defects and in mucus.[38,39] This process might further damage the epithelium and leads to the formation of Charcot-Leyden crystals.[39,40] In turn, these crystals further sustain the inflammation by enhancing the proinflammatory cytokine production from the epithelium and other inflammatory cells.[40,41] In addition, the deposition of these highly stable crystals leads to a secondary neutrophilic inflammation and NETosis, which leads to further damage to the tissue or epithelium and may lead to resistance to therapeutic interventions with glucocorticoids.[40-43]

TREATMENT APPROACHES AND UNMET NEEDS

Type 2 immune reactions in CRSwNP have been associated with asthma comorbidity, severity, and recurrence of nasal polyps after systemic GCS or surgical treatment.[6] Frequent oral GCS boosts per year and repeated surgeries are therefore a clear hint for type 2 CRSwNP. Other type 2 signs are the presence of comorbid late-onset asthma, the diagnosis of AERD, histopathologic findings of eosinophils in former surgery specimen, and finally elevated blood eosinophil counts and increased polyclonal serum IgE concentrations.[44]

Current treatment approaches have been extensively described in national and international guidelines. Within the patients with type 2 CRSwNP, there is a group of about 25% to 30% of subjects who will relapse after oral GCSs or conventional sinus surgery, and often need several surgeries in lifetime; more than 60% of these patients also have late-onset asthma. Patients with CRSwNP, who relapse after systemic GCSs and/or adequate

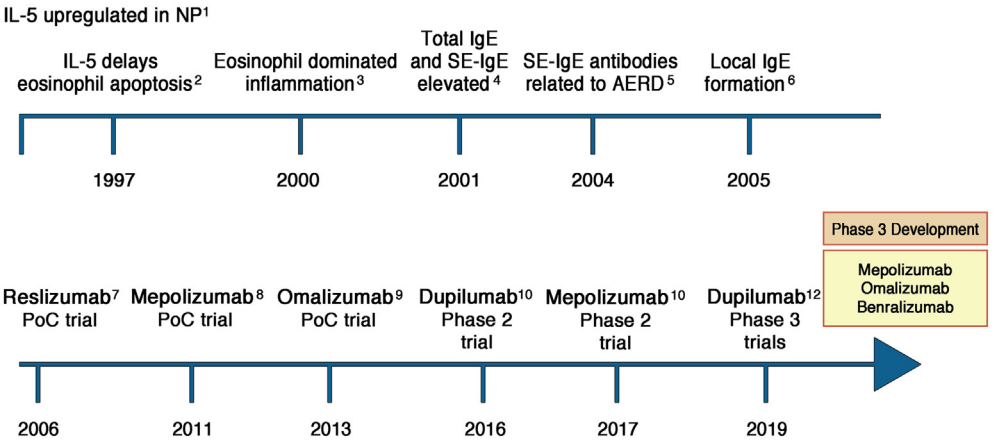

FIG 1. Recognition of type 2 cytokines and IgE in CRSwNP and the development of biologic therapies over time. *NP*, Nasal polyp; *SE-IgE*, specific IgE to *S aureus* enterotoxins.

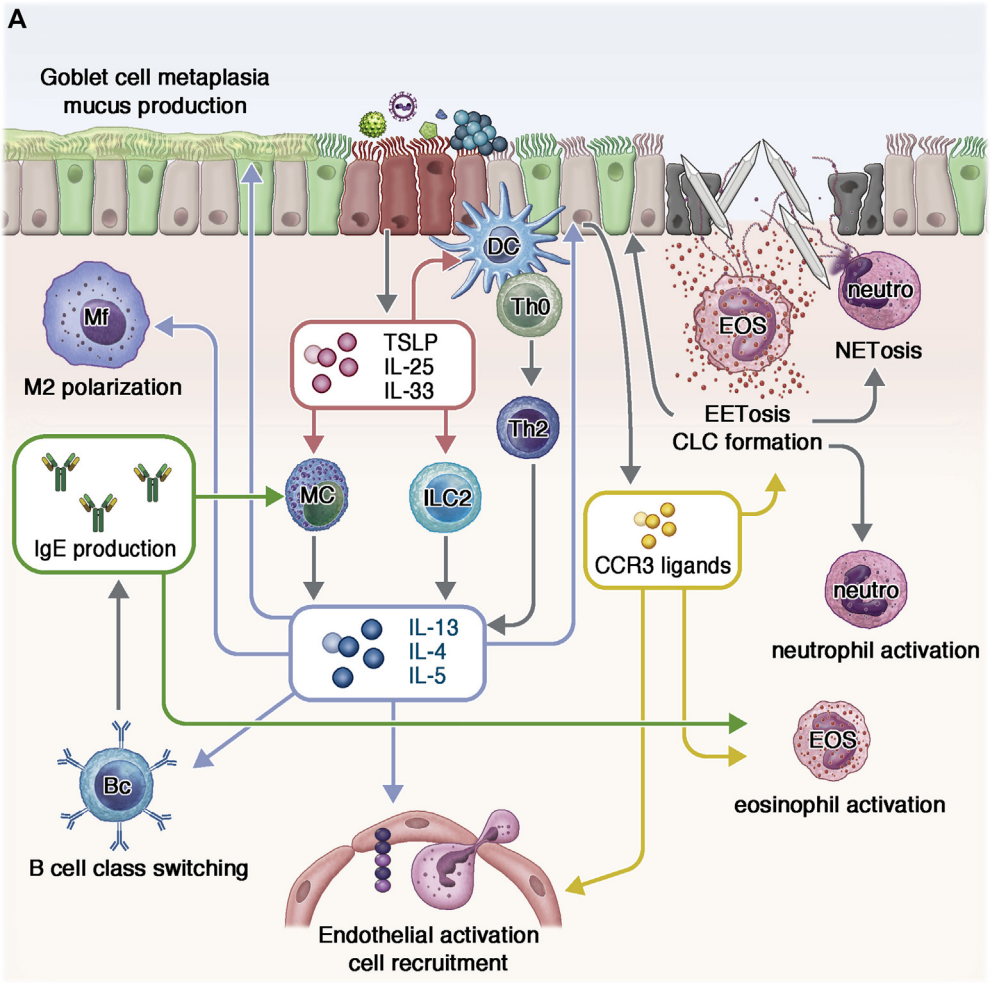

FIG 2. Biologics and their targets in type 2 inflammation in CRSwNP. **A,** Target cytokines in type 2 immune reactions. **B,** Cells and mediators of type 2 inflammation and corresponding biologics. *CCR-3*, C-C motif chemokine receptor 3; *CLC*, Charcot-Leyden-Crystal; *DC*, dendritic cell; *EOS*, eosinophils; *IL-4Rα*, IL-4 receptor alpha; *IL-13Rα*, IL-13 receptor alpha; *neutro*, neutrophils.

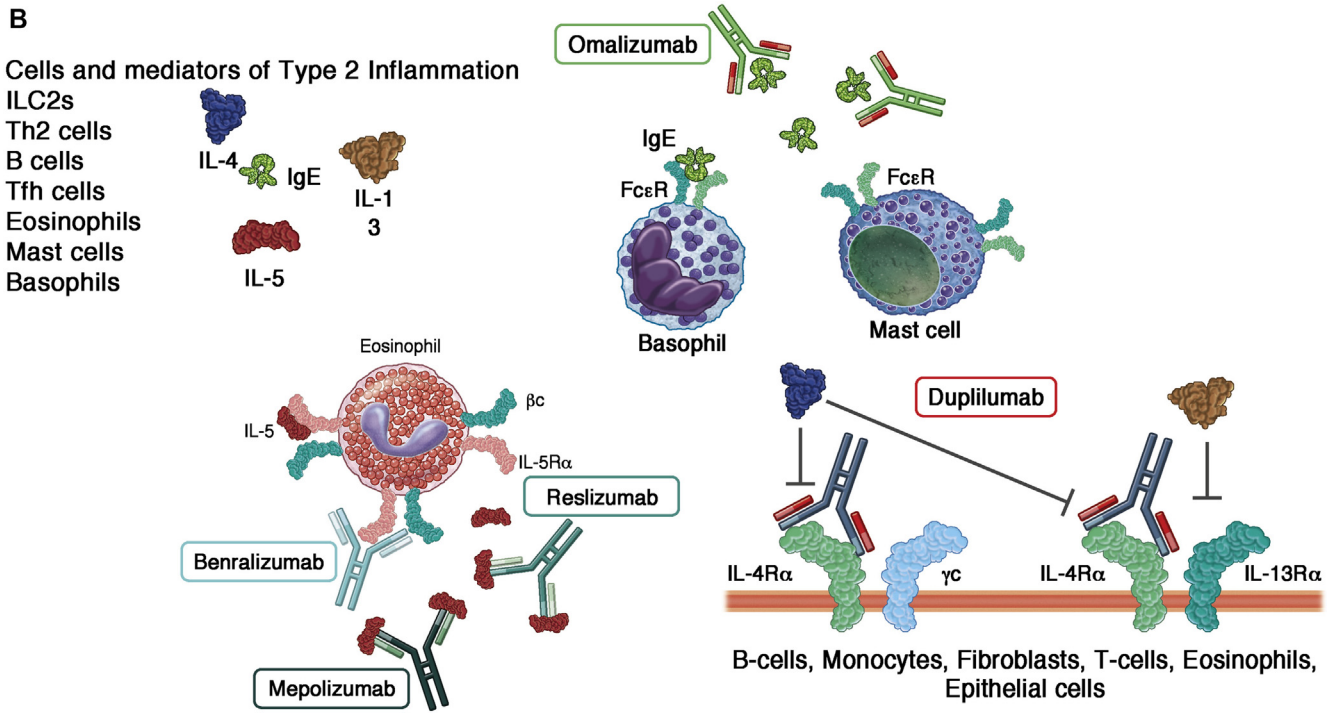

FIG 2. Continued.

surgery, and are symptomatic and relevantly impaired in their quality of life (QOL), should be identified as severe and uncontrolled, and eventually treated with biologics as an innovative option. It needs to be remembered that treatment with systemic GCSs or surgery is both associated with adverse events, specifically when GCSs are applied repeatedly or long-term,[45] and possible complications, specifically when surgeries are performed repeatedly. Major complications are reported in about 0.5% to 1% of sinus surgeries.[46] The expectations in terms of efficacy and duration from these interventions as well as adverse events and complications need to be discussed with the patient, and alternatives (eventually biologics) proposed, and patients should be actively involved in the decision process.

Identified targets and biologics in phase 3 trials for CRSwNP

The current phase 3 studies, published, submitted for publication, or running momentarily, are targeting the IL-5 pathway and eosinophils, IgE and mast cell activation, or the IL-4/IL-13 pathway with a broader activity. Here, we summarize the development in the understanding of the pathways, the effects of antagonism, and the available clinical trials over time (Figs 1 and 2 and Tables I and II).[47-54]

IL-5 AND THE TRANSMEMBRANE IL-5 RECEPTOR

European patients with CRSwNP were initially defined by high IL-5 tissue concentrations and eosinophilic inflammation, whereas patients with CRSsNP showed low IL-5 levels, but increased IL-17 concentrations in many patients.[55] Increased IL-5 expression was confirmed also in US and Asian patients with CRSwNP,[56,57] although to a lower extent and in competition with the IL-17 pathway in Asia.[58] CRSwNP is characterized by infiltration of cells producing IL-5, including not only $CD4^+$ T cells, mast cells, and eosinophils[59] but also innate cells such as $CD117^+$ $IL\text{-}1RI^+$ ILC2s.[12] In CRSwNP, IL-5 concentrations are associated with comorbid asthma and disease recurrence compared with patients without these comorbidities. IL-5 acts via the high-affinity IL-5R, which is composed of an IL-5–specific α chain and a β chain shared with the receptor for GM-CSF and IL-3. The IL-5R α chain is expressed by eosinophils and basophils while soluble IL-5 receptor alpha (IL-5Rα) is generated as a result of alternative splicing[60]; its binding does not lead to signal transduction and has an antagonistic effect on IL-5 signaling.[61] The expression of soluble IL-5Rα is increased in CRSwNP and correlates to disease severity and eosinophil counts, whereas the expression of transmembrane IL-5Rα is downregulated and inversely correlated to eosinophils and soluble IL-5Rα expression.[62] As discussed before, tissue eosinophils show a prolonged survival compared with peripheral blood eosinophils and obviously can survive on low IL-5 concentrations[38]; the role of soluble IL-5R is not entirely clear, and they may serve as a reservoir for IL-5.

ANTAGONIZING EOSINOPHIL ACTIVATION IN CRSwNP

The basis of the development of anti–IL-5 receptor mAb strategies was the acknowledgment of the crucial importance of this cytokine in promoting eosinophil development, activation, and survival,[63] which also was demonstrated in nasal polyps; IL-5, but not IL-3 or GM-CSF, was crucial for the prevention of eosinophil apoptosis.[38] Interestingly, there are some contradictory studies and doubts on the role of eosinophils, which may need further explanation.[64,65] However, mepolizumab, reslizumab, and benralizumab reduce blood and tissue eosinophil counts, reduce corticosteroid dependence and

TABLE I. Biologics in CRSwNP: Overview on available studies

Study	Primary outcome parameters, duration	Dosing	Inclusion criteria	AE
Reslizumab		**Inhibits IL-5**		
Gevaert et al,[47] 2006 Phase 2	Reduction in NPS 36 wk	Single intravenous infusion of 3 mg/kg or 1 mg/kg or placebo	18 y or older. Massive bilateral nasal polyps (grade 3 or 4) or recurrent nasal polyps after surgery	Most common AE was upper respiratory tract infection
Mepolizumab		**Inhibits IL-5**		
Gevaert et al,[48] 2011 Phase 2	Reduction in NPS 8 wk	Two single intravenous infusions (28 d apart) of 750 mg of mepolizumab or placebo	Subjects must have had failure of standard care for CRSwNP. Diagnosis of CRSwNP was based on the European position paper on rhinosinusitis	Most common AE was common cold
Bachert et al,[49] 2017 Phase 2	Number of patients who no longer met the criteria for surgery 4 wk after end of treatment (based on NPS and VAS) 25 wk	Intravenous infusion of 750 mg of mepolizumab or matched placebo every 4 wk for 6 doses	18-65 y. Bilateral nasal polyposis. CRS symptoms despite use of INCS for at least 2 mo. Minimum bilateral nasal polyp score of 5 of a maximum of 8 for both nostrils. At least 2 of the following symptoms before screening: nasal obstruction or nasal discharge and/or facial pain or pressure and a reduction/loss of smell	Most frequent AEs were headache and nasopharyngitis. AEs with >5% incidence were oropharyngeal pain, back pain, influenza, and pyrexia
Omalizumab		**Binds free IgE**		
Pinto et al,[50] 2010 Phase 2	Quantitative measurement of sinus inflammation on imaging 6 mo	Subcutaneous injection of omalizumab or matched placebo every 2 or 4 wk based on total serum IgE levels and body weight	18-75 y. CRS symptoms for more than 12 wk. Evidence of inflammation on nasal endoscopy and sinus CT scan. Serum total IgE between 30 and 700 IU/mL. This study was not restricted to nasal polyps, but also included CRS without polyps	No side effects or AEs reported
Gevaert et al,[51] 2013 Phase 2	Reduction in NPS 16 wk	Subcutaneous injection of omalizumab or matched placebo every 2 or 4 wk based on total serum IgE levels and body weight	18 y or older. CRSwNP and comorbid asthma for more than 2 y. Serum total IgE between 30 and 700 IU/mL	Most common AEs were common cold, frontal headache, and otisis media
POLYP 1[52] POLYP 2[52] Phase 3	Coprimary end points: reduction of NPS and NCS (nasal congestion score) 24 wk	Subcutaneous injection of omalizumab or matched placebo every 2 or 4 wk based on total serum IgE levels and body weight	18-75 y. Weight: 30-150 kg. 30-1500 IU/mL serum IgE. Persistent bilateral nasal polyps. Impaired health-related QOL. Nasal congestion score (NCS) ≥2. Total NPS ≥5. SNOT-22 score ≥20	Most common AEs were headache, injection-site reactions, arthralgia, dizziness, and upper abdominal pain. No anaphylaxis, Churg-Strauss syndrome, and/or hypereosinophilic syndrome was observed
Dupilumab		**Blocks IL-4Rα receptor**		
Bachert et al,[53] 2016 Phase 2	Reduction in NPS 16 wk	Subcutaneous injection of 600-mg loading dose of dupilumab or matched placebo followed by 15 weekly doses of 300 mg of dupilumab or matched placebo	18-65 y. Bilateral nasal polyposis. CRS symptoms despite use of INCS for at least 2 mo. Minimum bilateral NPS of 5 of a maximum of 8 for both nostrils. At least 2 of the following symptoms before screening: nasal obstruction or nasal discharge and/or facial pain or pressure and a reduction/loss of smell	AEs reported by 25 of 30 patients in the placebo and 30 of 30 in the dupilumab group. Most frequent AEs were mild-to-moderate nasopharyngitis (33% vs 47%), injection-site reactions (7% vs 40%), and headache (17% vs 20%). No serious AEs were considered to be related to dupilumab

(Continued)

TABLE I. *(Continued)*

Dupilumab			**Blocks IL-4Rα receptor**	
Bachert et al,[54] 2019 Phase 3	Coprimary end points: reduction of NPS and NCS (nasal congestion score) 24 wk + 24-wk follow-up	Subcutaneous injection of 300 mg of dupilumab every 2 wk or placebo for 24 wk	18 y or older. Bilateral nasal polyposis. CRS symptoms despite use of INCS before randomization. Had received systemic corticosteroids in the preceding 2 y. Previous sinonasal surgery. Minimum bilateral NPS of 5 of a maximum of 8 for both nostrils. At least 2 of the following symptoms before screening: nasal congestion or obstruction and either loss of smell or nasal discharge	Pooled safety population: the incidence of AEs was lower in the dupilumab group than in the placebo group. Most commonly reported AEs were nasopharyngitis, nasal polyps (worsening nasal polyps, need for surgery or systemic corticosteroids), headache, asthma (worsening of asthma), epistaxis, and injection-site erythema; these events were more frequent with placebo
Bachert et al,[54] 2019 Phase 3	Coprimary end points: reduction of NPS and NCS (nasal congestion score) 52 wk + 12-wk follow-up	Subcutaneous injection of 300 mg every 2 wk for 52 wk or 300 mg every 2 wk for the first 24 wk followed by injections every 4 wk until reaching 52 wk, or received placebo	18 y or older. Bilateral nasal polyposis. CRS symptoms despite use of INCS before randomization. Had received systemic corticosteroids in the preceding 2 y. Previous sinonasal surgery. Minimum bilateral NPS of 5 of a maximum of 8 for both nostrils. At least 2 of the following symptoms before screening: nasal congestion or obstruction and either loss of smell or nasal discharge	Cough, bronchitis, arthralgia, accidental overdose, and injection-site reactions were slightly more frequent in the dupilumab group. Treatment-emergent adverse events of worsening of nasal polyps and asthma and arthralgia occurred more frequently in patients who switched from dupilumab every 2 wk to every 4 wk
Ongoing trials				
Mepolizumab				
NCT03478930[10] Phase 3			Estimated study completion date: March 18, 2020 https://clinicaltrials.gov/ct2/show/NCT03478930	
SYNAPSE[11] Phase 3			Study completion date: December 11, 2019. Results not yet published https://clinicaltrials.gov/ct2/show/NCT03085797	
Benralizumab				
OSTRO[12] Phase 3			Estimated study completion date: August 7, 2020 https://clinicaltrials.gov/ct2/show/NCT03401229	
ORCHID[13] Phase 3			Estimated study completion date: July 12, 2022 https://clinicaltrials.gov/ct2/show/NCT04157335	

AE, Adverse event; *INCS*, intranasal corticosteroid.

asthma exacerbations, and are approved for the treatment of severe eosinophilic asthma.[66-68] Their effectiveness also has been demonstrated for CRSwNP, with mepoliumab and benralizumab currently in phase 3 trials. With the IL-5 antagonism, also secondary phenomena such as eosinophil extracellular trap release from activated eosinophils and Charcot-Leyden-crystal formation with the consecutive recruitment of neutrophils[41] should be avoided; however, it is unclear how long Charcot-Leyden-crystals can persist in the tissue and maintain a neutrophilic inflammation.

In a double-blind placebo-controlled, randomized (DBPCR), 2-center safety and pharmacokinetic study, 24 subjects with bilateral CRSwNP were randomized to receive a single intravenous infusion of reslizumab, a humanized antihuman IL-5 mAb, at 3 mg/kg or 1 mg/kg or placebo.[47] A single injection of reslizumab reduced the nasal polyp score (NPS) for 4 weeks in about half the patients, but had no significant effect on symptoms, and nasal IL-5 levels (>40 pg/mL) seemed to predict the response to treatment. Blood eosinophil numbers and concentrations of ECP were reduced up to 8 weeks after treatment in serum and nasal secretions. In patients with asthma with elevated blood eosinophils (≥400 cells/μL), the presence of CRSwNP based on the patient-reported medical history seemed to signal the effective reduction of clinical asthma exacerbations and improvements in lung function in patient-reported asthma control and asthma QOL.[69] There is currently no further development for reslizumab in CRSwNP.

The proof-of-concept (PoC) study in severe CRSwNP was performed with mepolizumab, a humanized anti–IL-5 mAb, provided in 2 intravenous injections of 750 mg with a month interval.[48] Thirty patients with a mean NPS of 5 or more, or recurrence after surgery, refractory to corticosteroid therapy, were randomized in a DBPCR study versus placebo: 50% has comorbid asthma, 25% had AERD, and 75% had former sinus surgery at baseline. Change from baseline in NPS was assessed at 8 weeks, 4 weeks after the last dose, indicating a response in 60% of the verum- versus 10% of the placebo-treated patients (by 1 score point or more); the computed tomography (CT)

TABLE II. Biologics in selected CRSwNP studies—efficacy parameters

Reslizumab

Gevaert et al[47]		Baseline	4 wk	12 wk
NPS	1 mg/kg	6 (6)	Decreased in 4 of 8 (2 of 8) patients	Decreased in 5 of 8 (1 of 8) patients
	3 mg/kg	5 (6)	Decreased in 3 of 8 (2 of 8) patients	Decreased in 1 of 8 (3 of 8) patients
	Comment: Levels in nasal secretions were significantly higher in the responders than in the nonresponders. Logistic regression analysis revealed that increased nasal IL-5 levels (>40 pg/mL) predict the response to anti–IL-5 treatment.			

Mepolizumab

Gevaert et al[48]	Baseline	8 wk	Bachert et al[49]	Baseline		25 wk
NPS	5.2 (5.5)	−1.30	% of patients requiring surgery	100%		30% (10%)
Improvement % patients		50%	% of patients improved by >1 point in NPS			50% (27%)
CT scan improvement		>50% (<20%)	SNOT-22 questionnaire	51.5 (49.5)		−13.2
Blood eosinophil counts (10^3/mL)		−332	Blood eosinophil counts (cells/μL)	500 (470)		−330
			PnIF (L/min)	101		+26.7
			Nasal polyposis severity VAS scores	Rhinorrhea	6.2	−2.4
				Mucus in throat	6.0	−2.1
				Nasal blockage	7.9	−1.8
				Loss of smell	9.0	−1.9
			Note: Baseline blood eosinophil counts did not affect the responder rate and could not be used to identify responders.			

Omalizumab

Pinto et al[50]	Baseline	6 mo	Gevaert et al[51]	Baseline	16 wk
% of OMU CT opacification	76.1%	60.0% (difference between groups was not statistically significant)	NPS	6 (6)	−2.79
Note: No other markers showed statistically significant differences between groups.			Lund-Mackay CT score	17.5 (16.5)	−3.5
			Symptom scores*	NA	NA
			SF-36 physical health score	48 (50)	NA
			RSOM-31:	NA	NA
			AQLQ	5.75 (4.73)	−0.54
			Note: Lund-Mackay CT scan score improved significantly in allergic subjects. The AQLQ score improved significantly in the nonallergic subjects.		

POLYP 1[52]	Baseline	16 wk	24 wk	POLYP 2[52]	Baseline	16 wk	24 wk
NPS	6.2 (6.3)	−0.95	−1.02	NPS	6.4 (6.1)	−0.91	−0.59
Nasal congestion score	2.4 (2.5)	−0.57	−0.54	Nasal congestion score	2.3 (2.3)	−0.59	−0.50
TNSS	8.6 (9.3)	NA	−0.85	TNSS	8.7 (8.4)	NA	−2.09
Loss-of-smell score	2.5 (2.8)	NA	−0.33	Loss-of-smell score	2.6 (2.8)	NA	−0.45
Postnasal drip	1.7 (2)	NA	−0.56	Postnasal drip	1.6 (1.8)	NA	−0.55
Runny nose	1.9 (2.1)	NA	−0.43	Runny nose	1.9 (1.9)	NA	−0.62
SNOT-22	59.8 (60.5)	NA	−16.12*	SNOT-22	59.2 (59.8)	NA	−15.04*
UPSIT	12.8 (13.9)	NA	+3.81	UPSIT	12.8 (13.1)	NA	+3.87

Dupilumab

Bachert et al[53]	Baseline	16 wk
NPS	5.9 (5.7)	−1.6
Improvement by >1 point in NPS		50%
% of maxillary sinus volume occupied by disease (CT)	71% (76.3%)	−32.2%
Lund-Mackay CT score	18.6 (18.7)	−8.9
Sinusitis symptom severity VAS	6.4 (6.4)	−2.1
Nasal congestion or obstruction in the morning	1.7 (1.7)	−0.7

(Continued)

TABLE II. *(Continued)*

		Dupilumab	
Anterior rhinorrhea	AM	1 (1.1)	−0.6
	PM	1 (1.2)	−0.5
Posterior rhinorrhea	AM	1.1 (1.4)	−0.46
	PM	1 (1.4)	−0.4
Loss of smell	AM	2.4 (2.8)	−1.3
	PM	2.4 (2.8)	−1.2
SNOT-22		41.4 (40.6)	−18.1*
Nocturnal awakenings		0.9 (1.0)	−0.4
PnIF (L/min)	AM	98.4 (109.2)	+33.1
	PM	105.2 (121.3)	+33.4
UPSIT		12.8 (15.6)	+13.4
Total serum IgE (IU/mL)		139.7 (195.3)	−56.3%
Plasma eotaxin-3 (pg/mL)		64 (61.6)	−45.5%
TARC		NA	NA

Liberty NP 24 Bachert et al[54]	Baseline	24 wk
NPS	5.64 (5.86)	−2.06
Nasal congestion/ obstruction score	2.26 (2.45)	−0.89
TNSS	6.10	−2.60
Lund-Mackay CT score	18.55 (19.55)	−7.44
SNOT-22	48 (50.87)	−21.12*
UPSIT	14.68 (14.44)	+10.56
Loss-of-smell score	2.70 (2.73)	−1.12
PnIF (L/min)	98.59 (83.52)	+40.41
Rhinorrhea daily symptom score	NA	−0.62
Rhinosinusitis (VAS)	7.42 (7.96)	−3.20
Note: Symptoms worsened after discontinuation of dupilumab at week 24.		

Liberty NP 52 Bachert et al[54]		Baseline q2w	24 wk q2w	52 wk q2w
NPS		6.07 (5.96)	−1.81	−2.39
Nasal congestion/ obstruction score		2.48 (2.38)	−0.87	−0.98
TNSS		6.08	−2.45	NA
Lund-Mackay CT score		18.42 (17.65)	−5.12	NA
SNOT-22		50.16 (53.48)	−17.37	−20.96*
UPSIT		13.46 (13.78)	+10.52	NA
Loss-of-smell score		2.81 (2.72)	−0.98	NA
PnIF (L/min)		80.96 (87.47)	36.64	NA
Rhinorrhea daily symptom score		NA	0.59	NA
Rhinosinusitis (VAS)		8.24 (7.98)	−2.93	NA
Serum	Total IgE (IU/mL)	211.79 (228.59)	−153.15	−221.01
	Periostin (ng/mL)	109.70 (113)	−35.77	−40.69
	TARC (pg/mL)	372.27 (370.20)	−130.58	−143.44
Plasma	Eotaxin-3 (pg/mL)	70.61 (90.84)	−35.59	−40.81
Nasal	ECP (ng/mL)	60.3 (54.7)	−16.9	NA
	Total IgE (IU/mL)	49.43 (19.91)	−39.53	NA
	IL-5 (pg/mL)	24.77 (20.39)	−24.77	NA
	Eotaxin-3 (pg/mL)	69.94 (57.00)	−94.41	NA
	Note: Symptom score improved up to week 52. Systemic corticosteroid use was 74% and effective surgery 83% lower in the dupilumab group than in the placebo group. FEV_1 (+0.21) and ACQ score (−0.82) significantly improved in patients with asthma.			
	NPS and Lund-Mackay CT scan improvements from week 24 to week 52 in SINUS-52 were numerically greater in patients who continued the dupilumab every 2-wk regimen than in those who switched to a dose every 4 wk.			

ACQ, Asthma Control Questionnaire; *AQLQ*, Asthma Quality of Life Questionnaire; *NA*, not available/not applicable; *PnIF*, peak nasal inspiratory flow; *RSOM-31*, 31-item Rhinosinusitis Outcome Measuring Instrument; *SF-36*, 36-item short form survey; *TARC*, thymus and activation regulated chemokine; *TNSS*, Total Nasal Symptom Score (nasal congestion, loss of smell, anterior and posterior rhinorrhea); *UPSIT*, University of Pennsylvania Smell Identification Test.
*Reached minimal clinically important difference (≥8.9 points).

scan confirmed this response. Blood eosinophils and serum, but not nasal ECP concentrations, dropped as expected. These results indicated potential for mepolizumab when applied for a longer period, without safety concerns.

A second study with mepolizumab versus placebo included 107 patients receiving 750 mg intravenously every 4 weeks for a total of 6 doses in addition to daily topical GCS treatment.[49] Patients were required to be eligible for surgery, being refractory to standard-of-care steroid therapy, and have undergone at least 1 previous undefined nasal polyp removal surgery. The mean baseline NPS was higher than 6, and 80% of subjects also had asthma. Different from other studies, the primary end point was

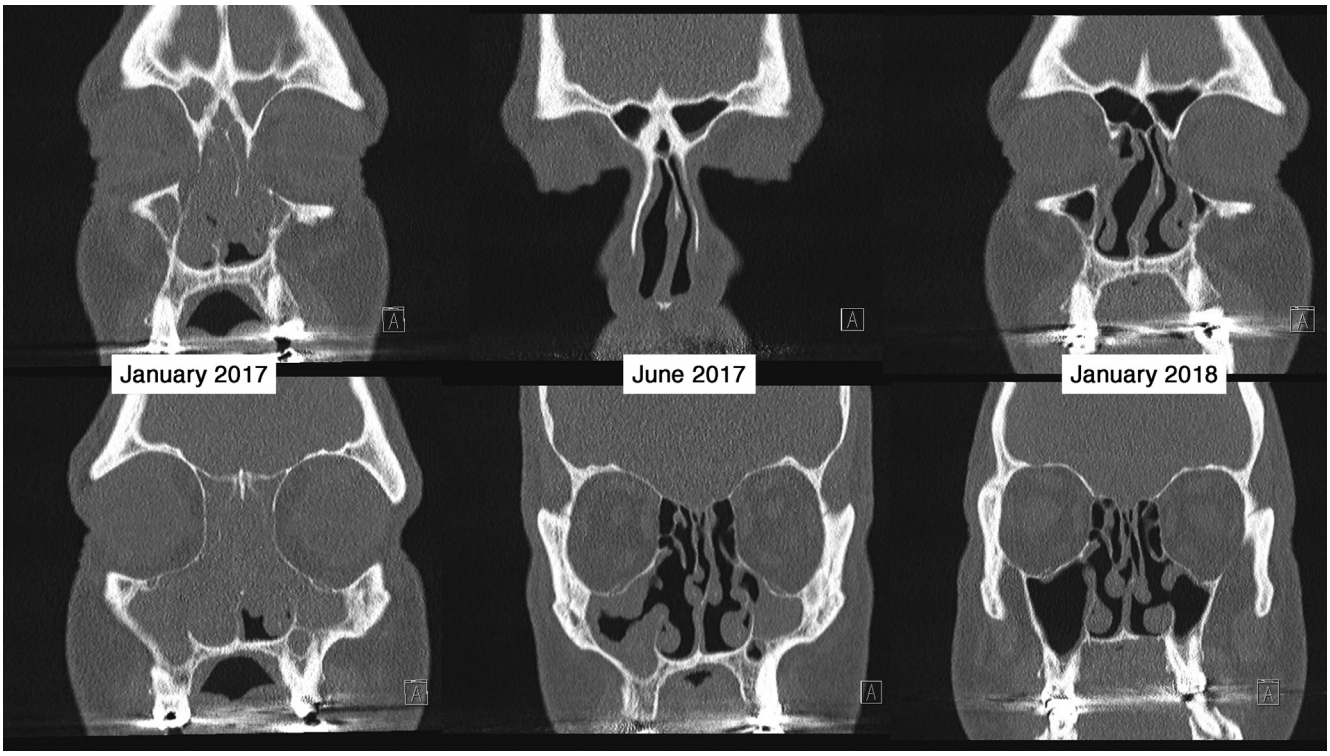

FIG 3. CT scans over 1 year in a patient with CRSwNP under dupilumab.

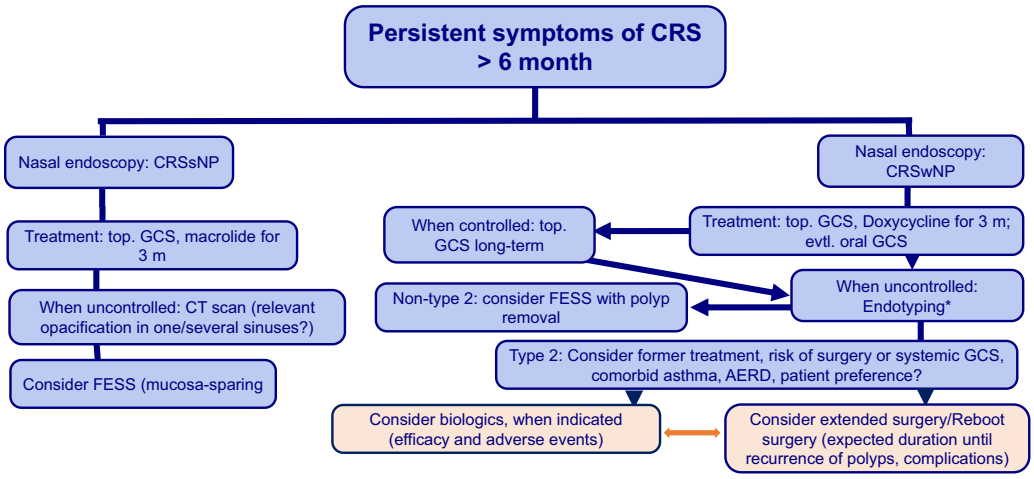

FIG 4. Care pathways for CRS and severe type 2 CRSwNP. *FESS*, Functional endoscopic sinus surgery. Modified from Bachert and Zhang.[107] *Type 2 markers: comorbid late-onset asthma, AERD, eosinophils in former biopsy, increased blood eosinophils, elevated total IgE, polysensitization.

the number of patients no longer requiring surgery at week 25 based on a composite score of NPS and nasal polyp severity visual analogue scale (VAS). A significantly greater proportion of patients in the mepolizumab group compared with the placebo group no longer required surgery at end of trial: 30% versus 10% ($P < .006$). This was complemented by a significant improvement in nasal polyp severity VAS, NPS (50% vs 27% improved by at least 1 score point), all individual VAS symptom scores, and 22-item Sino-Nasal Outcome Test (SNOT-22) score (changes baseline to end of treatment: mean, 23 vs 11) in the mepolizumab group compared with the placebo group; safety profiles were comparable. There was no association between baseline eosinophil counts and achieving a 1-point or greater improvement in endoscopic NPS at week 25. A phase 3 trial "Effect of mepolizumab in severe bilateral nasal polyps: SYNAPSE" using 100 mg subcutaneously, changing dosage and application, was just finished, and results are to be expected soon. The diagnosis of eosinophilic CRS in subjects with severe

asthma treated with mepolizumab significantly improved systemic corticosteroid–sparing effects, change from baseline fractional exhaled nitric oxide, and symptoms.[70]

For benralizumab, an IL-5 receptor antagonist, no PoC or phase 2 studies have been published in CRSwNP. Efficacy and safety of benralizumab in severe eosinophilic asthma have been demonstrated in 2 DBPCR phase 3 studies, the SIROCCO[71] and CALIMA[72] studies; in these studies, 15% to 20% of the patients also reported nasal polyps, which were again shown to predict enhanced efficacy irrespective of baseline blood eosinophil counts.[73] There are currently 2 phase 3 studies ongoing in severe CRSwNP, the OSTRO and the ORCHID studies (see Table I). Benralizumab 30 mg subcutaneous will be injected every 4 weeks for the first 3 doses (weeks 0 , 4, and 8) and every 8 weeks thereafter, with a total of 8 doses, versus placebo for 56 weeks and a 24-week follow-up for the first 200 subjects. Results are to be expected end of 2020 to 2021.

IgE: Role in nasal polyps

The role of IgE in CRSwNP, a late-onset disease, is not completely clear, because IgE is not or weekly related to (early-onset) atopy in patients with nasal polyps; CRSwNP appears to occur with similar frequency in atopic and nonatopic individuals. IgE is often strongly elevated in the sinus mucosa and the nasal polyps compared with controls, CRSsNP tissue, but also to allergic rhinitis mucosa.[14] IgE concentrations in CRSwNP tissue are strongly correlated with eosinophil markers,[5] and differ from allergic rhinitis in terms of their strong polyclonality.[74,75] However, polyclonal IgE in nasal polyp tissue is functional, as demonstrated by mast cell mediator release upon tissue exposure,[33] and is partially antagonized by IgG/IgG_4 antibodies also present within the tissue directed to the same antigens,[74] much alike the situation in specific immunotherapy for allergic rhinitis. In about 20% to 25% of patients with CRSwNP, specific IgE to *S aureus* enterotoxins is present within the nasal tissue and correlated to total IgE and eosinophil activation; furthermore, specific IgE to *S aureus* enterotoxins and high IgE tissue concentrations are associated with concomitant asthma and disease recurrence after surgical or systemic GCS treatment.[5,76] Recently, it has been shown that serum specific IgE to *S aureus* enterotoxins is associated with and predicts asthma severity and exacerbations.[77-79] This points to the fact that besides inhalant allergens, microbial allergens can trigger mast cell–mediated inflammation[76,80]; CRSwNP has a high colonization rate of up to 90% with *S aureus*.[81] High-affinity IgE receptors are expressed on mast cells, and typical mediators such as prostaglandins and leucotrienes released upon activation, but also low-affinity receptors expressed on dendritic cells and B cells, may help to mediate antigen presentation and finally more IgE antibody production.[82] Local class-switching to IgE[83] is supported by the expression of the immunoglobulin diversification enzyme activation-induced deaminase, local receptor revision, and B-cell differentiation into IgE-secreting plasma cells.[31]

OMALIZUMAB: ANTI-IgE TREATMENT

Omalizumab binds free IgE[84] and thus blocks the interaction of IgE with the high- affinity receptor FcεRI on mast cells and basophils.[85] The antibody also reduces FcεRI expression on basophils, mast cells, and dendritic cells[86] and therefore reduces allergen presentation, T_H2-cell activation, and T_H2-cell proliferation.[87] Targeting IgE-bearing B cells may further reduce the responsiveness to antigenic/allergen stimulation.[82] Omalizumab is also thought to suppress the production of prostaglandin D_2 and cysteinyl leucotrienes.[88] Finally, by interfering with the IgE-mediated mast cell degranulation, the release of mast cell–derived cytokines and their action on airway epithelium, B and T cells, and eosinophils is prevented. It has beneficial effects in patients with nasal polyposis and concomitant asthma, irrespective of their atopic status. The drug has been used for the treatment of patients with severe asthma longer than a decade, and has been well tolerated.[77]

With omalizumab indicated for severe asthma, and frequent nasal polyp comorbidity in this patient group, some case reports have been published early; uncontrolled studies in small cohorts have also been reported.[89] After a negative study,[50] possibly related to a suboptimal selection of patients, a first proof-of-concept randomized, double-blind, placebo-controlled study of allergic and nonallergic patients with nasal polyps was conducted.[51] All subjects suffered from comorbid asthma, although not severe. About 50% of the subjects suffered from AERD, and about 80% had former surgery, confirming the severity of disease. Interestingly, blood eosinophil counts were clearly elevated, with counts above 300/mL, whereas total serum IgE only ranged from 50 to 150 kU/L. Twenty-four subjects received 4 to 8 subcutaneous doses of omalizumab (n = 16) or placebo (n = 8), and the primary end point was the reduction in total nasal endoscopic polyp scores after 16 weeks. In this selective patient group, all suffering from asthma, the primary end point was not only significant but also impressively decreasing in the verum group by −2.67 score points ($P < .001$), whereas the placebo group showed no change. This was paralleled by a reduction of upper and lower airway symptoms, including the sense of smell, of sinus opacification in the CT scan evaluations, and an improvement in Asthma Quality of Life Questionnaire scores,[38] again without difference between atopic and nonatopic subjects. The drug was well tolerated. This PoC investigator-initiated study prompted phase 3 confirmation.

Two similar phase 3 trials, POLYP 1 and POLYP 2, have been recently performed to determine the safety and efficacy of omalizumab in patients with nasal polyps with an NPS of 5 or more.[52] Adult patients (n = 138 and 127) with inadequately controlled CRSwNP despite intranasal GCSs were randomized (1:1) to omalizumab or placebo for 24 weeks. At baseline, patients had an NPS above 6 and a SNOT-22 greater than or equal to 60, consistent with a substantial CRSwNP-related impairment in health-related QOL. More than 80% of patients were anosmic, more than 50% suffered mostly from nonsevere asthma, 27% reported AERD, 60% reported previous surgery, and 60% had at least 1 specific IgE sensitivity.

In both studies, the primary end point (NPS) was significant, with a reduction of about 0.9 to 1.1 points in the verum-treated subjects at week 24. In the second of the 2 studies, the placebo group also showed some, although not significant, change from baseline. NPS improvements of 1 or more and 2 or more points were observed in 56% and 31% of the patients, respectively. In parallel, nasal symptoms including loss of smell, postnasal drip,

and runny nose were significantly reduced, with nasal congestion as a coprimary end point; CRS-related QOL (SNOT-22) was significantly increased in both studies (−24.7 vs −8.6 [$P < .0001$] and −21.6 vs −6.6 [$P < .0001$]). Change from baseline (score, ~0.13) at week 8 for the smell test, University of Pennsylvania Smell Identification Test, was about 3.8 for omalizumab over placebo. Asthma-related QOL was also significantly improved in patients with concomitant asthma based on the percentage of patients achieving greater than or equal to 0.5 improvement in the Asthma Quality of Life Questionnaire score. There was a numeric reduction in steroid usage over the 24 weeks, but conclusions were not possible due to the small number of events in this limited time period. Omalizumab was well tolerated, with no unexpected safety concerns identified in the pooled data; asthma exacerbations were observed in 12% versus 4% of the placebo and verum patients, respectively, in line with the well- described effects of the drug in severe asthma. A just-finished open-label extension study of the above-mentioned POLYP studies will likely add to the knowledge in terms of long-term efficacy and tolerability in subjects with CRSwNP. Differences in populations across the trials could account for the less than expected reduction in the NPS in the phase 3 versus the PoC trials; however, the reduction of approximately 1 in the NPS resulted in a relevant improvement in the SNOT-22 score, questioning the relevance of such comparisons and the selection of adequate end points. Efficacy of omalizumab has also been demonstrated in real-life settings.[90]

TYPE 2 CRSwNP: ORCHESTRATED BY IL-4 AND IL-13

Accumulating evidence indicates that classical type 2 cytokines (IL-4, IL-5, IL-13) play critical roles in the induction of airway hyperreactivity, allergic inflammation, tissue remodeling, and mucus production in the airways.[91,92] CRSwNP is characterized by infiltration with IL-4– and IL-13–expressing cells, including T_H2 $CD4^+$ cells, ILC2 cells, basophils, and mast cells. T_H2 cells and ILC2s are the major producers of IL-13,[93,94] whereas IL-4 is produced mostly by basophils and T_H2 cells in asthmatic lungs.[95] IL-4 and IL-13 share many functional properties as a consequence of their use of a common receptor complex consisting of IL-13 receptor alpha 1 and IL-4 receptor alpha.[96] The ligation of receptors initiates the activation of the signal transducer and activator of transcription 6 pathway.[97] IL-13 receptor alpha 2 is a decoy receptor and was shown to be a powerful negative regulator of IL-4/IL-13 signaling in human fibroblasts.[98] Although they share the same signaling pathway, IL-4 and IL-13 have distinct roles in the pathogenesis of allergic immune responses. IL-4 has a prominent role in the regulation of T_H2 cells' survival and proliferation and IgE class-switch recombination, but has no major effect on airway hyperreactivity and mucus production in asthmatic airways.[99,100] IL-13 is functional in inducing airway hyperreactivity and mucus hyperproduction, as well as smooth muscle proliferation and fibrosis.[94,101] Both IL-4 and IL-13 and their respective receptor, IL-4Ra, are significantly elevated in CRSwNP; because IL-4Ra is expressed in submucosal glands, IL-4 and IL-13 may contribute to increased mucin production (mucin core protein 5A/5B) and tissue remodeling in CRSwNP.[26] IL-4 and IL-13 induce an alternative activation state of macrophages, a prominent feature of CRSwNP.[36]

THE anti–IL-4R ALPHA APPROACH: DUPILUMAB IN CRSwNP

With positive trials in severe asthma and atopic dermatitis, a first DBPCR study with dupilumab in CRSwNP refractory to intranasal corticosteroids was conducted in 2013/2014,[53] including a 16-week treatment period and a 16-week follow-up period in 60 adult patients (clinicaltrials.gov: NCT01920893). A subcutaneous dupilumab loading dose (600 mg) followed by 300 mg weekly doses was compared with placebo; all patients received mometasone furoate nasal spray for 16 weeks. About 60% of subjects had comorbid asthma, 70% were sensitized to at least 1 inhalant allergen, and 60% reported former surgery; the mean NPS was just below 6, and the mean SNOT-22 was about 41. Mean serum IgE level was about 140 IU/mL, and the mean blood eosinophil count was 410/mL. The reduction in NPS after 16 weeks was −1.9 points (95% CI, −2.5 to −1.2) versus −0.3 (95% CI, −1.0 to 0.4) for dupilumab versus placebo, paralleled by a difference in the CT sinus scan Lund-Mackey score of −8.8 (95% CI, −11.1 to −6.6; $P < .001$), in the SNOT-22 of −18.1 (95% CI, −25.6 to −10.6; $P < .001$), and in the sense of smell assessed by University of Pennsylvania Smell Identification Test of 14.8 (95% CI, 10.9 to 18.7; $P < .001$). Dupilumab resulted in significantly greater improvements in health-related QOL compared with placebo, based on SNOT-22, 36-item short form survey, EQ-5D, and VAS scores, and significantly lower adjusted annualized mean number of sick leave days as well as a significantly greater improvement in reduced productivity.[102] In patients with CRSwNP with comorbid asthma, a significant difference versus placebo was also observed for each of the individual ACQ-5 item scores.[103] The changes in CT scan sinus opacification were seen in all sinuses.[104] In line with the biologic effects, dupilumab significantly reduced total serum IgE and the serum eosinophil chemokine concentrations for thymus and activation-regulated chemokine and eotaxin-3, but had a temporary effect (increase due to reduced tissue migration) only on blood eosinophils. Type 2 biomarker concentrations also decreased in nasal secretions or nasal tissue for eotaxin-3 and total IgE, and for ECP, eotaxin-2, eotaxin-3, and pulmonary and activation-regulated chemokine, IgE, and IL-13, respectively.[105]

The first phase 3 trials in CRSwNP ever were reported just recently[54]; LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 were 2 multinational, multicenter, DBPCR studies assessing dupilumab versus placebo added to standard-of-care topical GCSs in adults with severe CRSwNP. Eligible patients had bilateral nasal polyps and symptoms despite intranasal GCSs, who received systemic GCSs in the preceding 2 years, or had sinonasal surgery ever. Patients were randomly assigned to subcutaneous dupilumab 300 mg or placebo every 2 weeks for 24 weeks (SINUS-24), or to dupilumab 300 mg every 2 weeks for 52 weeks, dupilumab every 2 weeks for 24 weeks and then every 4 weeks for the remaining 28 weeks, or placebo every 2 weeks for 52 weeks (SINUS-52; ClinicalTrials.gov NCT02912468 and NCT02898454). With an NPS of approximately 6 and a SNOT-22 baseline of approximately 50, 63% reported former surgery, 74% systemic GCSs in the last 2 years, 59% asthma, and 28% AERD. Dupilumab significantly improved the coprimary end points—NPS and nasal congestion score—in both studies (difference in NPS, −2.06;

95% CI, −2.43 to −1.69; $P < .0001$ in SINUS-24 and −1.80; 95% CI, −2.10 to −1.51; $P < .0001$ in SINUS-52 at week 24). In the SINUS-52 trial, a final reduction in the NPS over placebo of −2.40 (95% CI, −2.77 to −2.02; $P < .0001$) was achieved. Improvements in NPS and nasal congestion started within 4 to 8 weeks and continued up to the end of treatment in both studies, but relapsed with end of treatment. Differences in CT scan Lund-Mackay scores were −7.44 (95% CI, −8.35 to −6.53; $P < .0001$) in SINUS-24 and −5.13 (95% CI, −5.80 to −4.46; $P < .0001$) in SINUS-52 (the example of a patient is given in Fig 3). The smell test University of Pennsylvania Smell Identification Test score improved rapidly within the first 4 weeks in most of the verum-treated subjects, and by more than 10 points after 24 weeks; the SNOT-22 improved by −20.96 (95% CI, −25.03 to −16.89; $P < .0001$) over placebo after 52 weeks. Furthermore, there were remarkable reductions in actually applied systemic GCSs of 74% and in surgery of 83% in the dupilumab group compared with the placebo group. Of importance, the efficacy of dupilumab was shown both in the overall population and in subgroups with higher disease burden such as patients with comorbid asthma, nonsteroidal anti-inflammatory drug–exacerbated respiratory disease, or previous sinonasal surgery. The most common adverse events (nasopharyngitis, worsening of nasal polyps and asthma, headache, epistaxis, and injection-site erythema) were more frequent with placebo. Conjunctivitis was not induced in that patient group.[106]

DISCUSSION

Over the last 2 decades, the role of pathomechanisms active in CRSwNP has been developed and nowadays allows identifying new targets for intervention (Fig 1), possibly answering the unmet needs in CRSwNP. About a third of the patients with nasal polyps, suffering from uncontrolled disease and its comorbidities over decades, may at a certain time point be uncontrolled with the current therapeutic options. Although the growth of nasal polyps is incompletely understood, the inflammatory pathomechanisms have been at least partially elaborated, leading to polyp growth, but also to comorbidity; these pathomechanisms are primarily related to type 2. Biologics, developed for severe asthma or atopic dermatitis before, therefore have been applied to patients with CRSwNP in PoC studies, and phase 3 trials for dupilumab and omalizumab have recently been concluded successfully.[54] More biologics including mepolizumab and benralizumab are in phase 3 studies, and results will be published soon. With these achievements, patients with severe CRSwNP uncontrolled by standard-of-care measures today will have a new perspective for control. Impressive reductions in CRSwNP disease burden have been documented in terms of reduction of polyp mass, symptoms, sinus involvement, asthma symptoms and lung function tests, asthma control, and finally an increase in QOL, including work performance and absenteeism. Specifically, the ability to smell is not only of great importance for the patients but also is regained by many patients within just 4 to 8 weeks of treatment. It is apparent that biologics can and will compete with the current "last resort" of treatment, extended surgical procedures, and effects and side effects or complications have to be carefully balanced for these decisions, actively including the patients. It is very likely that future care pathways will combine biologics with surgery (Fig 4[107]), or build up on systemic GCSs, when the status of severe uncontrolled CRSwNP is reached. We have to keep in mind that CRSwNP is a chronic disease, bothering the patients for many decades, and care pathways have to be adapted to different situations during this natural course of disease.

However, there are many questions still to be answered, specifically referring to the selection of patients for biologics, specifically in combination with surgery or systemic GCSs, or in the selection of a specific biologic. What parameters reliably tell us how to identify responders among our patients, or stop further treatment with a specific biologic, and at which time points? We need to understand nonresponders to each of these biologics to select further treatment options, for example, another biologic; are those failures based on common principles or different per drug? Are there major differences in the efficacy, the effects on specific symptoms or asthma comorbidity, the time to onset, or the general responder rate between different biologics that would favor one of the others? In clinical practice already, today we realize that individual patients experience major amelioration under biologic therapy for their asthma, but not for their nasal polyps; how can we understand this phenomenon and what to do then? And also of importance, how will the community deal with the costs of these newly achieved possibilities?

BRIEF SUMMATION OF CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

The advent of biologics for the treatment of severe CRSwNP has without doubt met so far unmet needs and created new options for otherwise uncontrolled patients. The currently reported phase 3 trials have shown a great potential for those drugs, reducing the burden of disease at many levels from nasal symptoms to QOL, and more trials will be completed within a short time. Even new target molecules are already in development, and combinations of biologics may be helpful in certain patients with refractory severe uncontrolled disease. Finally, these new treatment options need to be implemented in daily clinical practice, based on care pathways taking into account efficacy and adverse events.

List of key concepts and therapeutic implications:

The cytokines IL-4, IL-5, and IL-13 are key cytokines of type 2 immune reactions.

Increased tissue and blood eosinophils as well as increased tissue and serum total IgE concentrations are typical signs of type 2 immune reactions.

Biologics targeting these cytokines and IgE have been developed for asthma, atopic dermatitis, and other type 2 diseases.

Because CRSwNP in the United States and Europe represents type 2 immune reactions in most patients, those biologics can also be applied to nasal polyp disease.

Omalizumab, mepolizumab, and dupilumab have been positively tested in PoC/phase 2 studies, and phase 3 trial results have been published or are awaiting publication.

Biologics may fulfill unmet needs in the treatment of CRSwNP, specifically in patients not controlled with topical and short-term systemic GCSs and/or surgery.

Biologics may be combined with surgery or short-term systemic GCSs, but care pathways based on available data still need to be elaborated and tested.

What do we know?

- **Type 2 cytokines including IL-4, IL-5, and IL-13 as well as IgE are expressed in about 80% of CRSwNP mucosal tissue.**
- **The expression of type 2 cytokines is associated with asthma comorbidity and recurrence of disease after surgery and systemic GCSs.**
- **Type 2 cytokines in CRSwNP are related to the inflammation found in most patients, with hypereosinophilia and IgE formation, and to the typical symptoms.**
- **Biologic therapies are currently in development for CRSwNP, targeting the type 2 cytokines and IgE, based on the above-mentioned rationale.**
- **PoC studies have been successfully performed in CRSwNP with mepolizumab, omalizumab, and dupilumab.**
- **Successful phase 3 trials have been published for dupilumab, and preliminary results have been communicated for omaliumab. Phase 3 trials are currently concluded or in process for mepolizumab and benralizumab, respectively; registration for dupilumab has been achieved in the United States and Europe.**
- **Dupilumab and omalizumab have been demonstrated to significantly reduce disease burden in patients with CRSwNP.**

What is still unknown?

- **Valid biomarkers for type 2 immune reactions in the sinuses are not defined; biomarkers to support the selection of biologic are completely lacking.**
- **Further subtyping of type 2 CRS using single-cell transcriptomics may be possible.**
- **Comparability of studies is limited because of the differences in included patient populations; head-to-head comparisons are lacking.**
- **Care pathways have been proposed, but not agreed upon; specifically, the indication for biologics versus surgery has not been defined.**
- **Prediction of the therapeutic response to a specific biologic is not currently feasible.**
- **No understanding of reasons for failure of specific biologics have been elaborated.**
- **No information is available on the selection of a second biologic in case a first one failed to reduce polyp burden.**
- **Stopping rules and valid clinical outcome parameters have not been defined.**

REFERENCES

1. Kohanski MA, Toskala E, Kennedy DW. Evolution in the surgical management of chronic rhinosinusitis: current indications and pitfalls. J Allergy Clin Immunol 2018;141:1561-9.
2. Bachert C, Zhang N, Hellings PW, Bousquet J. Endotype-driven care pathways in patients with chronic rhinosinusitis. J Allergy Clin Immunol 2018;141:1543-51.
3. Fokkens WJ, Lund VJ, Mullol J, Bachert C, Alobid I, Baroody F, et al. European Position Paper on Rhinosinusitis and Nasal Polyps 2012. Rhinol Suppl 2012;23:1-298.
4. Akdis CA, Bachert C, Cingi C, Dykewicz M, Hellings P, Naclerio RM, et al. Endotypes and phenotypes of chronic rhinosinusitis: a PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. J Allergy Clin Immunol 2013;131:1479-90.
5. Tomassen P, Vandeplas G, van Zele T, Cardell LO, Arebro J, Olze H, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. J Allergy Clin Immunol 2016;137:1449-56.
6. Bachert C, Zhang L, Gevaert P. Current and future treatment options for adult chronic rhinosinusitis: focus on nasal polyposis. J Allergy Clin Immunol 2015;136:1431-40.
7. Taillens JP. Nasal polyposis: value of blood eosinophils in surgical indications and in sinusal surgical therapy. Rev Laryngol Otol Rhinol (Bord) 1952;73:20-59.
8. Kaliner M, Wasserman SI, Austen KF. Immunologic release of chemical mediators from human nasal polyps. N Engl J Med 1973;289:277-81.
9. Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. Thorax 2000;55:S79-83.
10. Donovan R, Johansson SG, Bennich H, Soothill JF. Immunoglobulins in nasal polyp fluid. Int Arch Allergy Appl Immunol 1970;37:154-66.
11. Romagnani S. T-cell subsets (Th1 versus Th2). Ann Allergy Asthma Immunol 2000;85:9-18.
12. Van Crombruggen K, Taveirne S, Holtappels G, Leclercq G, Bachert C. Innate lymphoid cells in the upper airways: importance of CD117 and IL-1RI expression. Eur Respir J 2018;52.
13. Van Zele T, Claeys S, Gevaert P, Van Maele G, Holtappels G, Van Cauwenberge P, et al. Differentiation of chronic sinus diseases by measurement of inflammatory mediators. Allergy 2006;61:1280-9.
14. Bachert C, Gevaert P, Holtappels G, Johansson SG, Van Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. J Allergy Clin Immunol 2001;107:607-14.
15. Van Crombruggen K, Zhang N, Gevaert P, Tomassen P, Bachert C. Pathogenesis of chronic rhinosinusitis: inflammation. J Allergy Clin Immunol 2011;128:728-32.
16. Kohanski MA, Workman AD, Patel NN, Hung LY, Shtraks JP, Chen B, et al. Solitary chemosensory cells are a primary epithelial source of IL-25 in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2018;142:460-9.
17. Paris G, Pozharskaya T, Asempa T, Lane AP. Damage-associated molecular patterns stimulate interleukin-33 expression in nasal polyp epithelial cells. Int Forum Allergy Rhinol 2014;4:15-21.
18. Lan F, Zhang N, Holtappels G, De Ruyck N, Krysko O, Van Crombruggen K, et al. *Staphylococcus aureus* induces a mucosal type 2 immune response via epithelial cell-derived cytokines. Am J Respir Crit Care Med 2018;198:452-63.
19. Reh DD, Wang Y, Ramanathan M Jr, Lane AP. Treatment-recalcitrant chronic rhinosinusitis with polyps is associated with altered epithelial cell expression of interleukin-33. Am J Rhinol Allergy 2010;24:105-9.
20. Shaw JL, Fakhri S, Citardi MJ, Porter PC, Corry DB, Kheradmand F, et al. IL-33-responsive innate lymphoid cells are an important source of IL-13 in chronic rhinosinusitis with nasal polyps. Am J Respir Crit Care Med 2013;188:432-9.
21. Nagarkar DR, Poposki JA, Tan BK, Comeau MR, Peters AT, Hulse KE, et al. Thymic stromal lymphopoietin activity is increased in nasal polyps of patients with chronic rhinosinusitis. J Allergy Clin Immunol 2013;132:593-600.
22. Tojima I, Kouzaki H, Shimizu S, Ogawa T, Arikata M, Kita H, et al. Group 2 innate lymphoid cells are increased in nasal polyps in patients with eosinophilic chronic rhinosinusitis. Clin Immunol 2016;170:1-8.
23. Poposki JA, Klingler AI, Tan BK, Soroosh P, Banie H, Lewis G, et al. Group 2 innate lymphoid cells are elevated and activated in chronic rhinosinusitis with nasal polyps. Immun Inflamm Dis 2017;5:233-43.
24. Shi L-L, Song J, Xiong P, Cao PP, Liao B, Ma J, et al. Disease-specific T-helper cell polarizing function of lesional dendritic cells in different types of chronic rhinosinusitis with nasal polyps. Am J Respir Crit Care Med 2014;190:628-38.
25. Nagarkar DR, Poposki JA, Comeau MR, Biyasheva A, Avila PC, Schleimer RP, et al. Airway epithelial cells activate TH2 cytokine production in mast cells through IL-1 and thymic stromal lymphopoietin. J Allergy Clin Immunol 2012;130:225-32.
26. Zhang Y, Derycke L, Holtappels G, Wang XD, Zhang L, Bachert C, et al. Th2 cytokines orchestrate the secretion of MUC5AC and MUC5B in IL-5-positive chronic rhinosinusitis with nasal polyps. Allergy 2019;74:131-40.
27. Soyka MB, Wawrzyniak P, Eiwegger T, Holzmann D, Treis A, Wanke K, et al. Defective epithelial barrier in chronic rhinosinusitis: the regulation of tight junctions by IFN-γ and IL-4. J Allergy Clin Immunol 2012;130:1087-96.
28. Hulse KE, Norton JE, Suh L, Zhong Q, Mahdavinia M, Simon P, et al. Chronic rhinosinusitis with nasal polyps is characterized by B-cell inflammation and EBV-induced protein 2 expression. J Allergy Clin Immunol 2013;131:1075-83.
29. Kato A, Hulse KE, Tan BK, Schleimer RP. B-lymphocyte lineage cells and the respiratory system. J Allergy Clin Immunol 2013;131:933-57.

30. Gevaert P, Holtappels G, Johansson SG, Cuvelier C, Cauwenberge P, Bachert C. Organization of secondary lymphoid tissue and local IgE formation to *Staphylococcus aureus* enterotoxins in nasal polyp tissue. Allergy 2005;60:71-9.
31. Gevaert P, Nouri-Aria KT, Wu H, Harper CE, Takhar P, Fear DJ, et al. Local receptor revision and class switching to IgE in chronic rhinosinusitis with nasal polyps. Allergy 2013;68:55-63.
32. Baba S, Kondo K, Toma-Hirano M, Kanaya K, Suzukawa K, Ushio M, et al. Local increase in IgE and class switch recombination to IgE in nasal polyps in chronic rhinosinusitis. Clin Exp Allergy 2014;44:701-12.
33. Zhang N, Holtappels G, Gevaert P, Patou J, Dhaliwal B, Gould H, et al. Mucosal tissue polyclonal IgE is functional in response to allergen and SEB. Allergy 2011; 66:141-8.
34. Cao PP, Zhang YN, Liao B, Ma J, Wang BF, Wang H, et al. Increased local IgE production induced by common aeroallergens and phenotypic alteration of mast cells in Chinese eosinophilic, but not non-eosinophilic, chronic rhinosinusitis with nasal polyps. Clin Exp Allergy 2014;44:690-700.
35. Bochner BS, Klunk DA, Sterbinsky SA, Coffman RL, Schleimer RP. IL-13 selectively induces vascular cell adhesion molecule-1 expression in human endothelial cells. J Immunol 1995;154:799-803.
36. Krysko O, Holtappels G, Zhang N, Kubica M, Deswarte K, Derycke L, et al. Alternatively activated macrophages and impaired phagocytosis of *S. aureus* in chronic rhinosinusitis. Allergy 2011;66:396-403.
37. Pope SM, Brandt EB, Mishra A, Hogan SP, Zimmermann N, Matthaei KI, et al. IL-13 induces eosinophil recruitment into the lung by an IL-5- and eotaxin-dependent mechanism. J Allergy Clin Immunol 2001;108:594-601.
38. Simon HU, Yousefi S, Schranz C, Schapowal A, Bachert C, Blaser K. Direct demonstration of delayed eosinophil apoptosis as a mechanism causing tissue eosinophilia. J Immunol 1997;158:3902-8.
39. Gevaert E, Zhang N, Krysko O, Lan F, Holtappels G, De Ruyck N, et al. Extracellular eosinophilic traps in association with *Staphylococcus aureus* at the site of epithelial barrier defects in patients with severe airway inflammation. J Allergy Clin Immunol 2017;139:1849-60.
40. Persson EK, Verstraete K, Heyndrickx I, Gevaert E, Aegerter H, Percier JM, et al. Protein crystallization promotes type 2 immunity and is reversible by antibody treatment. Science 2019;364:6442.
41. Gevaert E, Delemarre T, De Volder J, Zhang N, Holtappels G, De Ruyck N, et al. Charcot-Leyden crystals promote neutrophilic inflammation in patients with nasal polyposis. J Allergy Clin Immunol 2020;145:427-30.
42. Wu D, Yan B, Wang Y, Zhang L, Wang C. Charcot-Leyden crystal concentration in nasal secretions predicts clinical response to glucocorticoids in chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2019;144:345-8.
43. Pothoven KL, Schleimer RP. The barrier hypothesis and Oncostatin M: restoration of epithelial barrier function as a novel therapeutic strategy for the treatment of type 2 inflammatory disease. Tissue Barriers 2017;5:e1341367.
44. Bachert C, Marple BF, Hosemann W, Cavaliere C, Zhang N. Endotypes of chronic rhinosinusitis: pathology and therapeutic implications. J Allergy Clin Immunol Pract 2020 [in press].
45. Hox V, Lourijsen E, Jordens A, Aasbjerg K, Agache I, Alobid I, et al. Benefits and harm of systemic steroids for short- and long-term use in rhinitis and rhinosinusitis: an EAACI position paper. Clin Transl Allergy 2020;10:1.
46. Hosemann W, Draf C. Danger points, complications and medico-legal aspects in endoscopic sinus surgery. GMS Curr Top Otorhinolaryngol Head Neck Surg 2013;12:06.
47. Gevaert P, Lang-Loidolt D, Stammberger H, Van Zele T, Holtappels G, Tavernier J, et al. Nasal interleukin-5 levels determine the response to anti-interleukin-5 treatment in nasal polyp patients. J Allergy Clin Immunol 2006;118:1133-41.
48. Gevaert P, van Bruaene N, Cattaert T, van Steen K, Van Zele T, Acke F, et al. Mepolizumab, a humanised anti-IL-5 monoclonal antibody, as treatment option for severe nasal polyposis. J Allergy Clin Immunol 2011;128:989-95.
49. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, et al. Reduced need for surgery in severe nasal polyposis with mepolizumab: a randomised trial. J Allergy Clin Immunol 2017;140:1024-31.
50. Pinto JM, Mehta N, DiTineo M, Wang J, Baroody FM, Naclerio RM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. Rhinology 2010;48:318-24.
51. Gevaert P, Calus L, Van Zele T, Blomme K, De Ruyck N, Bauters W, et al. Omalizumab is effective in allergic and non-allergic patients with nasal polyposis and co-morbid asthma. J Allergy Clin Immunol 2013;131:110-6.
52. Gevaert P, Omachi TA, Corren J, Mullol J, Han J, Lee SE, et al. Efficacy and safety of omalizumab in patients with chronic rhinosinusitis with nasal polyps: results from two, multicenter, randomized, double-blind, placebo-controlled phase III trials (POLYP 1 and POLYP 2). J Allergy Clin Immunol 2020 [in press].
53. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. JAMA 2016;315: 469-79.
54. Bachert C, Han JK, Desrosiers M, Hellings PW, Amin N, Lee SF, et al. Dupilumab efficacy and safety in severe chronic rhinosinusitis with nasal polyps in the multicentre, randomised, double-blind, placebo-controlled, parallel group phase 3 trials LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52. Lancet 2019;394: 1638-50.
55. Bachert C, Wagenmann M, Hauser U, Rudack C. IL-5 synthesis is upregulated in human nasal polyp tissue. J Allergy Clin Immunol 1997;99:837-42.
56. Allen JS, Eisma R, Leonard G, Kreutzer D. Interleukin-3, interleukin-5, and granulocyte-macrophage colony-stimulating factor expression in nasal polyps. Am J Otolaryngol 1997;18:239-46.
57. Zhang N, Holtappels G, Claeys C, Huang G, van Cauwenberge P, Bachert C. Pattern of inflammation and impact of *Staphylococcus aureus* enterotoxins in nasal polyps from southern China. Am J Rhinol 2006;20:445-50.
58. Wang M, Zhang N, Zheng M, Li Y, Meng L, Ruan Y, et al. Cross-talk between TH2 and TH17 pathways in patients with chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol 2019;144:1254-64.
59. Derycke L, Eyerich S, Van Crombruggen K, Pérez-Novo C, Holtappels G, Deruyck N, et al. Mixed T helper cell signatures in chronic rhinosinusitis with and without polyps. PLoS One 2014;9:e97581.
60. Yasruel Z, Humbert M, Kotsimbos TC, Ploysongsang Y, Minshall E, Durham SR, et al. Membrane-bound and soluble alpha IL-5 receptor mRNA in the bronchial mucosa of atopic and nonatopic asthmatics. Am J Respir Crit Care Med 1997; 155:1413-8.
61. Gevaert P, Bachert C, Holtappels G, Novo CP, Van der Heyden J, Fransen L, et al. Enhanced soluble interleukin-5 receptor alpha expression in nasal polyposis. Allergy 2003;58:371-9.
62. Gevaert P, Hellman C, Lundblad L, Lundahl J, Holtappels G, van Cauwenberge P, et al. Differential expression of the interleukin 5 receptor alpha isoforms in blood and tissue eosinophils of nasal polyp patients. Allergy 2009;64:725-32.
63. Clutterbuck EJ, Hirst EM, Sanderson CJ. Human interleukin-5 (IL-5) regulates the production of eosinophils in human bone marrow cultures: comparison and interaction with IL-1, IL-3, IL-6, and GMCSF. Blood 1989;73:1504-12.
64. Flood-Page PT, Menzies-Gow AN, Kay AB, Robinson DS. Eosinophil's role remains uncertain as anti-interleukin-5 only partially depletes numbers in asthmatic airway. Am J Respir Crit Care Med 2003;167:199-204.
65. Laidlaw TM, Prussin C, Panettieri RA, Lee S, Ferguson BJ, Adappa ND, et al. Dexpramipexole depletes blood and tissue eosinophils in nasal polyps with no change in polyp size. Laryngoscope 2019;129:E61-6.
66. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. N Engl J Med 2014;371:1198-207.
67. Nair P, Bardin P, Humbert M, Murphy KR, Hickey L, Garin M, et al. Efficacy of intravenous reslizumab in oral corticosteroid-dependent asthma [published online ahead of print October 15, 2019]. J Allergy Clin Immunol Pract. https://doi.org/10.1016/j.jaip.2019.09.036.
68. Bourdin A, Shaw D, Menzies-Gow A, FitzGerald JM, Bleecker ER, Busse WW, et al. Two-year integrated steroid-sparing analysis and safety of benralizumab for severe asthma. J Asthma 2019;26:1-9.
69. Weinstein SF, Katial RK, Bardin P, Korn S, McDonald M, Garin M, et al. Effects of reslizumab on asthma outcomes in a subgroup of eosinophilic asthma patients with self-reported chronic rhinosinusitis with nasal polyps. J Allergy Clin Immunol Pract 2019;7:589-96.
70. Numata T, Nakayama K, Utsumi H, Kobayashi K, Yanagisawa H, Hashimoto M, et al. Efficacy of mepolizumab for patients with severe asthma and eosinophilic chronic rhinosinusitis. BMC Pulm Med 2019;19:176.
71. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. Lancet 2016;388:2115-27.
72. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti–interleukin-5 receptor α monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet 2016;388: 2128-41.
73. Bleecker ER, Wechsler ME, FitzGerald JM, Menzies-Gow A, Wu Y, Hiesch I, et al. Baseline patient factor impact on the clinical efficacy of benralizumab for severe asthma. Eur Respir J 2018;18:52.
74. Shamji MH, Kappen J, Abubakar-Waziri H, Zhang J, Steveling E, Watchman S, et al. Nasal allergen-neutralizing IgG_4 antibodies block IgE-mediated responses: novel biomarker of subcutaneous grass pollen immunotherapy. J Allergy Clin Immunol 2019;143:1067-76.

75. Scheerens H, Smith A, Li O, Honigberg L, Harris JM, Holtappels G, et al. Elevated IgE M1 prime transcripts in nasal tissues in patients with nasal polyps and asthma. J Allergy Clin Immunol 2019;143:805-7.
76. Bachert C, Zhang N, Holtappels G, De Lobel L, Van Cauwenberge P, Shixi L, et al. Presence of IL-5 protein and IgE-antibodies to staphylococcal enterotoxins in nasal polyps is associated with co-morbid asthma. J Allergy Clin Immunol 2010;126:962-8.
77. Humbert M, Bousquet J, Bachert C, Palomares O, Pfister P, Kottakis I, et al. IgE-mediated multimorbidities in allergic asthma and the potential for omalizumab therapy. J Allergy Clin Immunol Pract 2019;7:1418-29.
78. Sintobin I, Siroux V, Holtappels G, Pison C, Nadif R, Bousquet J, et al. Sensitisation to staphylococcal enterotoxins and asthma severity: a longitudinal study in the EGEA cohort. Eur Respir J 2019;54.
79. Bachert C, Humbert M, Hanania NA, Zhang N, Holgate S, Buhl R, et al. *Staphylococcus aureus* and its IgE-inducing enterotoxins in asthma: current knowledge and research needs. Eur Respir J Jan 24; 2020.
80. Schreiber J, Bröker BM, Ehmann R, Bachert C. Non-atopic severe asthma might still be atopic: sensitization towards *Staphylococcus aureus* enterotoxins. J Allergy Clin Immunol 2019;143:2279-80.
81. Darisipudi MN, Nordengrün M, Bröker BM, Péton V. Messing with the Sentinels—the interaction of *Staphylococcus aureus* with dendritic cells. Microorganisms 2018;6.
82. Chan MA, Gigliotti NM, Dotson AL, Rosenwasser LJ. Omalizumab may decrease IgE synthesis by targeting membrane IgE+ human B cells. Clin Transl Allergy 2013;3:29.
83. Mechtcheriakova D, Sobanov Y, Holtappels G, Bajna E, Svoboda M, Jaritz M, et al. Activation-induced cytidine deaminase (AID)-associated multigene signature to assess impact of AID in etiology of diseases with inflammatory component. PLoS One 2011;6:e25611.
84. Holgate ST. New strategies with anti-IgE in allergic diseases. World Allergy Organ J 2014;7:17.
85. Mitchell PD, El-Gammal AI, O'byrne PM. Anti-IgE and biologic approaches for the treatment of asthma. Handb Exp Pharmacol 2017;237:131-52.
86. Macglashan DW, Bochner BS, Adelman DC, Jardieu PM, Togias A, Kenzie-White J, et al. Down-regulation of Fc(epsilon)RI expression on human basophils during in vivo treatment of atopic patients with anti-IgE antibody. J Immunol 1997;158:1438-45.
87. Holgate S, Casale T, Wenzel S, Bousquet J, Deniz Y, Reisner C. The anti-inflammatory effects of omalizumab confirm the central role of IgE in allergic inflammation. J Allergy Clin Immunol 2005;115:459-65.
88. Hayashi H, Mitsui C, Nakatani E, Fukutomi Y, Kajiwara K, Watai K, et al. Omalizumab reduces cysteinyl leukotriene and 9alpha,11beta-prostaglandin F2 overproduction in aspirin-exacerbated respiratory disease. J Allergy Clin Immunol 2016;137:1585-7.
89. Vennera Mdel C, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. Thorax 2011;66:824-5.
90. Tiotiu A, Oster JP, Roux P, Nguyen Thi PL, Peiffer G, Bonniaud P, et al. Omalizumab's effectiveness in severe allergic asthma and nasal polyps: a real-life study [published online ahead of print April 1, 2019]. J Investig Allergol Clin Immunol. https://doi.org/10.18176/jiaci.0391.
91. Manson ML, Säfholm J, James A, Johnsson AK, Bergman P, Al-Ameri M, et al. IL-13 and IL-4, but not IL-5 nor IL-17A, induce hyperresponsiveness in isolated human small airways [published online ahead of print December 2, 2019]. J Allergy Clin Immunol. https://doi.org/10.1016/j.jaci.2019.10.037.
92. Wynn TA. Type 2 cytokines: mechanisms and therapeutic strategies. Nat Rev Immunol 2015;15:271-82.
93. Price AE, Liang HE, Sullivan BM, Reinhardt RL, Eisley CJ, Erle DJ, et al. Systemically dispersed innate IL-13-expressing cells in type 2 immunity. Proc Natl Acad Sci 2010;107:11489-94.
94. Barlow JL, Bellosi A, Hardman CS, Drynan LF, Wong SH, Cruickshank JP, et al. Innate IL-13-producing nuocytes arise during allergic lung inflammation and contribute to airways hyperreactivity. J Allergy Clin Immunol 2012;129:191-8.e4.
95. Liang HE, Reinhardt RL, Bando JK, Sullivan BM, Ho IC, Locksley RM. Divergent expression patterns of IL-4 and IL-13 define unique functions in allergic immunity. Nat Immunol 2012;13:58-66.
96. LaPorte SL, Juo ZS, Vaclavikova J, Colf LA, Qi X, Heller NM, et al. Molecular and structural basis of cytokine receptor pleiotropy in the interleukin-4/13 system. Cell 2008;132:259-72.
97. Kuperman D, Schleimer R. Interleukin-4, interleukin-13, signal transducer and activator of transcription factor 6, and allergic asthma. Curr Mol Med 2008;8:384-92.
98. Andrews AL, Nasir T, Bucchieri F, Holloway JW, Holgate ST, Davies DE. IL-13 receptor alpha 2: a regulator of IL-13 and IL-4 signal transduction in primary human fibroblasts. J Allergy Clin Immunol 2006;118:858-65.
99. Silva-Filho JL, Caruso-Neves C, Pinheiro AAS. IL-4: an important cytokine in determining the fate of T cells. Biophys Rev 2014;6:111-8.
100. Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. Nat Rev Immunol 2014;14:247-59.
101. Seibold MA. Interleukin-13 stimulation reveals the cellular and functional plasticity of the airway epithelium. Ann Am Thorac Soc 2018;15:S98-102.
102. Bachert C, Hellings PW, Mullol J, Hamilos DL, Gevaert P, Naclerio RM, et al. Dupilumab improves health-related quality of life in patients with chronic rhinosinusitis with nasal polyposis. Allergy 2020;75:148-57.
103. Bachert C, Hellings PW, Mullol J, Naclerio RM, Chao J, Amin N, et al. Dupilumab improves patient reported outcomes in patients with chronic rhinosinusitis with nasal polyps and comorbid asthma. J Allergy Clin Immunol Pract 2019;7:2447-9.
104. Bachert C, Zinreich SJ, Hellings PW, Mullol J, Hamilos DL, Gevaert P, et al. Dupilumab reduces opacification across all sinuses and related symptoms in patients with CRSwNP [published online ahead of print October 31, 2019]. Rhinology. https://doi.org/10.4193/Rhin18.282.
105. Jonstam K, Swanson BN, Mannent L, Cardell LO, Tian N, Wang Y, et al. Dupilumab reduces local type 2 pro-inflammatory biomarkers in chronic rhinosinusitis with nasal polyposis. Allergy 2019;74:743-52.
106. Akinlade B, Guttman-Yassky E, de Bruin-Weller M, Simpson EL, Blauvelt A, Cork MJ, et al. Conjunctivitis in dupilumab clinical trials. Br J Dermatol 2019;181:459-73.
107. Bachert C, Zhang N. Medical algorithm: diagnosis and treatment of chronic rhinosinusitis. Allergy 2020;75:240-2.