



Biologics in Treatment for Chronic Rhinosinusitis with Comorbid Asthma

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Abstract

Purpose of Review It is reported that the prevalence of asthma is as high as 25% in patients with CRS, resulting in prolonged inflammation and recurrence. The remission of asthma has been found to be highly significant in contribution to the remission of CRS; hence, the usage of biologics treatment for asthma can be expanded towards the treatment for CRS with asthma. In this review, we summarized the usage of biologics in CRS with asthma treatment, their mechanisms, and future biologics in the development pipeline that would aid treatment for CRS with asthma.

Recent Findings Chronic rhinosinusitis is an inflammatory disease of the upper airway, and many are often accompanied by an asthma comorbidity of the lower airway. Chronic rhinosinusitis with comorbid asthma is commonly known as the manifestation of refractory rhinosinusitis, which is a major challenge of its treatment for otolaryngologists. In recent years, the treatment strategy of chronic rhinosinusitis with asthma has garnered increasing research interest. Particularly, the targeting of TH2 inflammatory cytokines, such as IgE, IL5, IL4, and IL13, has spawned an antibody-based biologics treatment against the disease. The availability of the biologics and their clinical efficacy has lent

confidence to the overall management of CRS with asthma in order to reduce the socioeconomic burden of the diseases.

Summary This paper reviews the current biologics available for chronic rhinosinusitis with asthma, focusing on its mechanism and clinical efficacy, as well as highlighting promising biologics currently in trials that may aid in the treatment of the disease.

Introduction

Chronic rhinosinusitis (CRS) is a chronic inflammatory disease defined by the appearance of two or more of the following symptoms for more than 12 weeks, one of which being nasal congestion or rhinorrhea, with or without facial pain or loss of smell [1••]. Symptom-based CRS has affected 5.5 to 28% of the population worldwide [2–5], greatly affecting the quality of life of those suffering from it. A study by Gliklich and Metson further found that CRS had an even greater impact on social functioning than angina or chronic heart failure [6]. Routine treatments of chronic rhinosinusitis include drug therapy, nasal lavage, and functional sinus surgery (FESS) and supported by conventional drug therapy including intranasal steroids, leukotriene antagonists, antihistamines and antiallergic drugs, and systemic corticosteroids [7–9]. Although many treatment strategies for CRS are available, there are still a significant portion of patients whose symptoms remained uncontrolled despite treatment, termed refractory rhinosinusitis [1••]. Recently, with unified airway theory gaining traction in the research of chronic airway inflammation, more potential connections between the upper and lower airway, including pathophysiology and epidemiology of the inflammation, have been found [10, 11]. It is reported that the prevalence of asthma is as high as

25% in patients with CRS while only hovering around 5% in the general population [12]. Patients with CRS with nasal polyps (CRSwNP) frequently presented comorbid asthma at the same time [13•], often showing similar pathophysiology and eosinophilia characteristics at both the upper and lower airway [14]. Many studies have established that, in tissue with increased eosinophils, type 2 inflammatory patterns and increased TH2 cytokines like IL-4, IL-13, and IL-5 are highly expressed, which activate eosinophils and mast cells and stimulate mast cells producing IgE, resulting in prolonged inflammation and recurrence [15]. The remission of asthma has been found to be highly significant in contribution to the remission of CRS; hence, the usage of biologics treatment for asthma can be expanded towards the treatment for CRS with asthma. The usage of biologics, such as omalizumab, dupilumab, and mepolizumab, has been documented to being successfully used in the treatment of CRS with asthma (Table 1). Therefore, in this review, we summarized the usage of biologics in CRS with asthma treatment, their mechanisms, and future biologics in the development pipeline (Fig. 1) that would aid treatment for CRS with asthma.

Biologics for the Treatment of CRS With and Without Asthma

Anti-IgE Biologics

IgE is an important downstream mediator in the pathogenesis of CRS with asthma. Patients with allergic inflammatory diseases in the airway often presented with high levels of IgE [26–28]. Therefore, treatments that lowers IgE, or the effects of IgE, would suppress IgE-mediated chronic inflammation and reduce the symptoms of the inflammation, as a means to control the disease. The current approved anti-IgE biologics available is omalizumab [29, 30].

Table 1. Main biologic medications for CRS, asthma, or CRS with asthma

CRS				
Drug	Target	CRS with asthma Clinical trials	Treatment group	Primary outcome
Omalizumab	IgE	Therese Bidder, et al. (2018) [16••]	Patients with both CRSwNP and severe refractory allergic asthma	The median SNOT-22 was improved and showed no differences, between the omalizumab and surgery treated groups; the ACQ-7 was decreased
Dupilumab	IL-4RA	Bachert, C., et al. (2019) [19]	Patients aged 18 to 65 years with bilateral NP and CRS despite INCS including 35 patients with asthma	Improved endoscopic NP score sense of smell, Lund-Mackay score, and CRSwNP disease severity SNOT-22, ACQ-5
Mepolizumab	IL-5	Numata, T., et al. (2019) [21••]	28 patients with severe asthma including 16 patients with ECRS	In patients with CRSwNP and comorbid asthma Improved systemic corticosteroid-sparing effects and other clinical variables
Reslizumab	IL-5	No published studies		
Benralizumab	IL-5RA	No published studies		
Asthma				
Drug	CRS Treatment group	Primary outcome	Clinical trials	Primary outcome
Omalizumab	24 adults with CRSwNP with asthma; serum IgE 30–700 µg/mL	Improvement in NPS, LMS, airway symptoms and quality of life scores	Holgate, S.T et al. (2004) [18]	246 patients aged 12–75 with severe asthma
Dupilumab	Objects with bilateral CRSwNP and symptoms despite intranasal corticosteroid use	Improvement in SNOT-22 scores, nasal obstruction, UPSIT olfactory score, NPS, LMS, FEV1, and reduction of exacerbation	Wenzel, S et al. (2016) [20]	Moderate to severe eosinophilic asthma (>300 cells per µL)
Mepolizumab	Patients aged 18 to 70 years with recurrent nasal		Pavord, I.D et al. (2012) [23]	Severe eosinophilic asthma (≥150 cells in asthma exacerbations
Clinical trials				
				Gevaert, P et al. (2013) [17•]
				Bachert, C et al. (2019)
				Bachert et al. (2017) [22]
				Gevaert, P., et al. (2016) No published studies

Table 1. (Continued)

Drug	CRS		Asthma	
	Treatment group	Primary outcome	Clinical trials	Treatment group
Reslizumab	polypsis requiring surgery	Reduction in the need for surgery; improvement in symptoms	Intravenous reslizumab is safe. The number of eosinophils in serum and nasal secretions was reduced. While only half of the subjects who received reslizumab showed improvement in nasal polyp scores and lasted for 4 weeks merely	per μL at screening or ≥ 300 cells per μL in past year)
	24 patients with bilateral nasal polyps			Castro, M et al. (2015) [24] Moderate to severe eosinophilic asthma (≥ 400 cells per μL) and symptoms; mild improvement in FEV_1 and steroid sparing Considerable improvement in asthma exacerbations; mild improvement in FEV_1 and symptoms
Benralizumab	No published studies			Bleecker, E.R et al. (2016) [25] Severe eosinophilic asthma (≥ 300 cells per μL) Considerable improvement in asthma exacerbations and in FEV_1 and steroid sparing

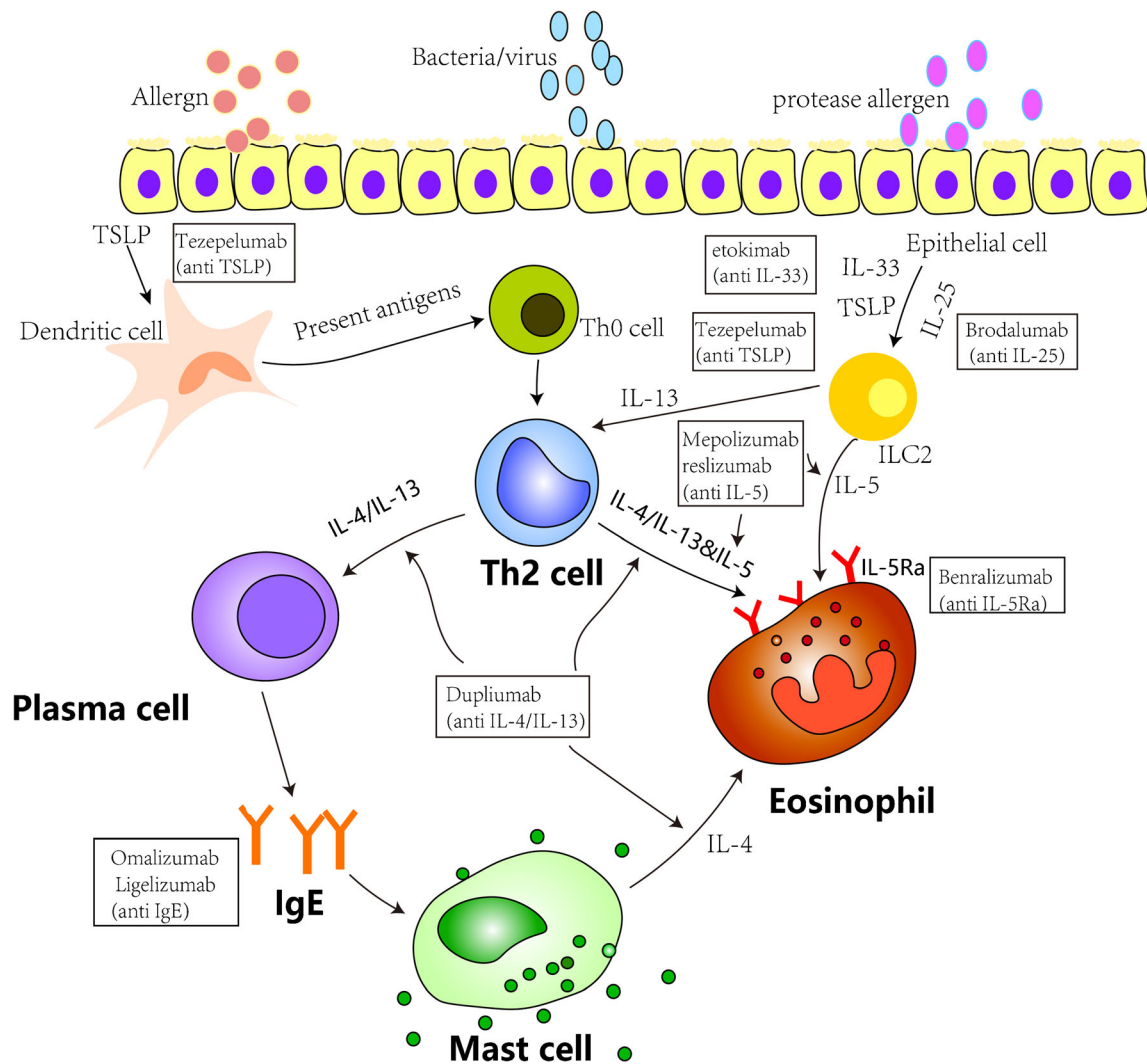


Fig. 1.. The pathophysiology and biologics' targets of CRS comorbid with asthma

Omalizumab

Omalizumab is a humanized IgG monoclonal antibody that inhibits the binding of IgE to high-affinity IgE receptors (FcεRI) by binding to the IgE instead, thus preventing the activation of basophils and mast cells [17•, 29, 31, 32]. It has been licensed to treat allergic asthma since 2014. In a meta-analysis of 25 randomized controlled trials by Normansell R et al. [33], omalizumab was considered statistically significant in reducing acute episodes of asthma and reducing hospitalization as an ancillary drug to ICS. Only 16% of the omalizumab group patients suffered exacerbation over 16 to 60 weeks, compared to 26% in the placebo group. A double-blind randomized clinical trial by Gevaert et al. [17•] also reported that subcutaneous injection of omalizumab (4 to 8 doses) can significantly reduce the total nasal endoscopic polyp score of allergic patients in 16 weeks (−2.67,

$P=0.001$). Additionally, regardless of allergic status, omalizumab can improve airway symptoms [nasal congestion ($P=0.003$), rhinorrhea ($P=0.003$), loss of smell ($P=0.004$), wheezing ($p=0.02$), and dyspnea ($P=0.020$)] and quality of life scores. A prospective study on omalizumab by Therese Bidder et al. [16••] found that in the early stages of omalizumab treatment, there existed a rapid improvement in SNOT-22 at the 4th week of treatment, and it could be maintained with continued treatment. The study also found no difference in the SNOT-22 median after 16 weeks of subcutaneous administration of omalizumab compared with the surgical group. This trial firstly showed that there was a parallel relationship between ACQ-7 and the improvement of SNOT-22 after omalizumab treatment, further implicating the use of asthma biologics for treatment of CRS with asthma.

Anti-IL-4 and Anti-IL-13 Biologics

IL-4 and IL-13 are important upstream drivers of many atopic diseases with predominant type 2 inflammation. Compared with anti-IgE biologics, the former showed a greater potential in reducing airway inflammation [28••]. IL-4 and IL-13 play an important role in the pathogenesis of CRS with asthma, in which they shared a part of the receptors and signal transduction pathways and are closely related to plasma cell activation, IgE synthesis, and eosinophil activation [34, 35]. Furthermore, they were also found to stimulate Th0 cell to differentiate into Th2 cells [36] and to promote the adhesion of eosinophils to vascular endothelium and their migration to local tissue inflammatory sites [37], perpetuating type 2 inflammation. Moreover, IL-4 was also found to promote the differentiation of B cells into plasma cells which further enhanced IgE generation [38, 39]. As IL-4 and IL-13 shared similar pathways in their activation of type 2 inflammation, biologics developed against them were hoped to serve dual role of suppressing the effect of both factors. The anti-IL-4 and anti-IL-13 biologics currently approved include dupilumab, tralokinumab, MEDI9314, and SAR-156596. However, only dupilumab is allowed to be used in the treatment of CRS.

Dupilumab

Dupilumab is a humanized monoclonal antibody that binds to IL-4 α receptor and block the signal transduction of both IL-4 and IL-13. A double-blind randomized clinical trial by Wenzel et al. [40] showed a decrease in acute episodes of asthma in dupilumab (300mg) group by 87% (OR 0.08; 95% CI 0.02 to 0.28; $P<0.001$) compared with in placebo group, and most patients' asthma symptoms and lung function improved following treatment. However, a drawback is that dupilumab showed significantly higher rates of injection site reactions, nasopharyngitis, nausea, and headache compared to placebo [40]. Bachert et al. published three double-blind placebo-controlled trials on the clinical efficacy of dupilumab between 2016 and 2019, further showing the efficacy of dupilumab [19, 41, 42]. Furthermore, in a multicenter phase III clinical trial conducted in 2019 (SINUS-24 and SINUS-52), they recruited subjects with bilateral CRSwNP and symptoms despite intranasal corticosteroid use and surgical treatment. A total of 724 patients were enrolled in both trials, and there was a

significant improvement in the SNOT-22 scores, nasal obstruction, UPSIT olfactory score, nasal polyp score (NPS), Lund-Mackay CT scores (LMS), and asthma prognosis (FEV1 and the control of exacerbation) [1, 19, 41, 42]. Hence, the finding confirmed the efficacy of dupilumab, which currently stands as the only approved IL4/IL13 biologics for CRS with asthma.

Anti-IL-5 Biologics

IL-5 belongs to the β c cytokine family which interacts with hematopoietic cells to regulate their survival, proliferation, differentiation, and activation [43]. It was found that IL-5 is closely related to the increase and activation of eosinophil in allergy, parasitic infections, and hyper eosinophilic syndromes [44]. IL-5 can specifically activate eosinophils and then promote their proliferation as well as prolong their lifespan at the local inflammatory sites in the tissues [44, 45]. Therefore, suppressing IL-5 levels and action via anti-IL-5 biologics is useful in reducing eosinophilic infiltration in chronic airway inflammation. The currently approved anti-IL-5 biologics include mepolizumab, reslizumab, and benralizumab.

Mepolizumab

Mepolizumab is an anti-IL-5 humanized monoclonal antibody which can bind to IL-5, interfering its binding with receptors expressed in the eosinophils and basophils [46]. A randomized, double-blind, placebo-controlled clinical trial by Ortega et al. [47] in 2014 reported that mepolizumab intravenously or subcutaneously showed a significant improvement in the FEV1, George's Respiratory Questionnaire (SGRQ), and the 5-item Asthma Control Questionnaire (ACQ-5). However, blood eosinophil counts (ECP), IL-5, and total IgE levels had no difference between the two groups. A study to estimate the efficacy of mepolizumab for CRSwNP by Bachert et al. [22] showed that, compared with the placebo group, the mepolizumab group significantly reduced the surgical treatment rate [mepolizumab group 16 (30%) vs. placebo group 5 (10%); $P=0.006$]. Additionally, VAS scores for rhinorrhea, nasal congestion, mucus, and hyposmia; SNOT-22 scores; and peak nasal inspiratory flow were improved significantly. However, it was to be noted that there was no statistical difference between the two groups in terms of sense of smell or lung function. Nevertheless, mepolizumab's effect on asthma is definite [45••] and stands as a suitable treatment for CRS with asthma.

Reslizumab

Similar to mepolizumab, reslizumab is also an anti-IL-5 biologics [48]. Reslizumab has been approved by the FDA in 2016 for the additional maintenance treatment of severe asthma with eosinophil phenotype in patients over 18 years of age. There are several clinical trials in 2015 and 2016 to show the effect of reslizumab on eosinophilic airway inflammation. These include two phase III clinical trials investigating severe asthma patients whose symptoms was inadequately controlled by medium-to-high doses of inhaled corticosteroid and suffered from at least one exacerbation in the previous year from multiple regions and centers. With the blood

eosinophils ≥ 400 cells/ μ L or < 400 cells/ μ L, respectively [24, 49], both of them showed that patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations. Moreover, reslizumab was well tolerated with fewer adverse events when compared to the placebo group. Another randomized, double-blind, placebo-controlled study by Gevaert et al. [50] further showed that intravenous reslizumab is safe, and the 8-week treatment reduced the number of eosinophils in serum and nasal secretions. However, only half of the subjects who received reslizumab showed improvement in nasal polyp scores, which lasted for only 4 weeks [50]. Nevertheless, the improvement still warrants further investigation into the usage of reslizumab in the treatment of CRS with asthma.

Benralizumab

Benralizumab is an IL-5Ra-directed cytolytic monoclonal antibody that has been shown to be effective for both eosinophilic asthma and chronic rhinosinusitis [51]. It has completed its phase 3 trials which assessed its safety and efficacy for patients with severe, uncontrolled eosinophilic asthma, including the SIROCCO and CALIMA trials [25, 52, 53]. Among the 2295 patients in the trials, they found that benralizumab significantly reduced the annual exacerbation rate (AER) and improved the pre-bronchodilator FEV1 (Q4W and Q8W) and total asthma symptom score (Q8W only). However, despite its efficacy, there was few data currently available on benralizumab's efficacy and safety in CRS treatment. A randomized control trial for evaluation of benralizumab treatment in 336 patients with CRSwNP (NCT03450083 and NCT03401229) is currently ongoing [54].

Other Biologics Currently in Development Pipeline

Other Anti-IgE Biologics

Even though omalizumab has been an established anti-IgE therapy for the treatment of allergic diseases, there are still a portion of patients who are not sensitive to it. Hence, new anti-IgE biologics are still exploring such as ligelizumab (QGE031) whose affinity with IgE is higher than omalizumab [55]. Currently, the reports on QGE031 are mainly in the treatment of spontaneous urticaria. In 2016, Gauvreau, G.M et al. [56] published a paper that supported the clinical development of QGE031 as a treatment of asthma. They found that QGE031 might has greater efficacy than omalizumab on inhaled and skin allergen responses in patients with mild allergic asthma after a double-blind, parallel-group multicenter study that compared the clinical efficacy, IgE levels, and Fc ϵ RI expression with omalizumab.

IL-22 Treatment

IL-22 is produced by Th22 cells which sometimes terms to be a protective role against the development of antigen-induced eosinophilic airway inflammation [57–59], while in the research of Besnard et al. [60] showed

that IL-22 plays a critical role in the initiation of immune responses induced by subcutaneous sensitization. Recently, new biologic targets IL22, fezakinumab (FZ), which was mainly researched in the field of atopic dermatitis (AD) have been introduced. In view of similarity of the inflammatory features between AD and asthma, Badi, Y et al. [61•] conducted a study which proved that FZ response signatures were significantly enriched in the blood of asthmatics versus healthy subjects ($P < 0.05$). This is an illuminating result that sheds light on a new potential pathway for treating asthma and even respiratory inflammatory diseases.

Antagonist of IL-25

IL-25 (also known as IL-17E) is a member of the TH17 cytokine and has been reported to play a variety of roles in enhanced expression of TH2-related factors [62, 63]. Previous studies found that in NP mucosa from patients with CRS with NPs, the IL-25 expression was upregulated compared with uncinate process tissue from control subjects and those with CRSsNPs. What is more, anti-IL-25 treatment could reduce the number of polyps, mucosal edema thickness, collagen deposition, and infiltration of inflammatory cells, such as eosinophils and neutrophils and the expression of local inflammatory cytokines [64, 65]. Ballantyne et al. [66•] reported that by administering anti-IL-25 mAb during the sensitization phase resulted in significantly reduced levels of the level of Th2 cytokines such as IL-5 and IL-13, eosinophil infiltration, goblet cell hyperplasia, and serum IgE secretion and prevented AHR, a crucial feature of clinical asthma [18, 20]. Brodalumab is a human anti-IL-17 receptor A (IL-17RA) monoclonal antibody that inhibits the biological activity of IL-17A, IL-17F, IL-17E, and other isoforms and has been approved for the treatment of psoriasis. And clinical trial of brodalumab in uncontrolled asthma was terminated due to a lack of observed efficacy in a pre-specified interim analysis (NCT01902290).

Antagonist of TSLP

Early in 1994, TSLP was first identified as an IL-7-like cytokine, which can strongly activate dendritic cells (DCs) through the TSLP-TSLPR and OX40L-OX40 signaling pathways to promote Th2 differentiation. Chen et al. investigated that neutralizations of TSLP can reverse the process of airway Th2 inflammations, structural alterations, and AHR to methacholine in a chronic HDM-induced asthma model [21••]. In addition, the immune responses induced by TSLP can be inhibited with the treatment with OX40L-blocking antibodies substantially in a mice model, including IgE production, cytokine secretion, and Th2 inflammatory cell infiltration [23]. Tezepelumab (AMG 157/MEDI9929) is a human monoclonal antibody specific for TSLP. In a phase 2, randomized, double-blind, placebo-controlled trial, among adult patients with uncontrolled asthma, the authors compared subcutaneous tezepelumab at three dose levels with placebo over a 52-week treatment period. The primary end point was the annualized rate of asthma exacerbations (events per patient-year) at week 52. They found that tezepelumab had lower rates of clinically significant

asthma exacerbations than those who received placebo (NCT02054130) [67].

In another clinical trial (NCT01405963) [68•], the researchers found tezepelumab-reduced allergen-induced bronchoconstriction and indexes of airway inflammation before and after allergen challenge. It was a relatively small double-blind, placebo-controlled trial in 31 patients with mild allergic asthma. The patients were received three monthly doses of AMG 157 (700 mg) or placebo intravenously. Whether anti-TSLP therapeutics will have clinical value in other allergic diseases remains to be demonstrated.

Antagonist of IL-33

IL-33 (also labeled as IL-1F11) is a member of the IL-1 family and has been first reported in 2005 [69]. IL-33 can be rapidly released from epithelial cells upon stress or cellular damage. And it induces Th2 inflammation instead of Th1-associated cytokines via binding to its receptor, ST2 [70]. Both IL-33 protein and the IL-33 mRNA levels in CRS were significantly different from those in the control mucosa [71•]. Previous studies reported that the deficiency of IL-33 is responsible for the decrease of eosinophilia and AHR in the mouse model with airway allergic inflammation [72]. There is a phase 2a clinical trial of etokimab (ANB020), an anti-33 monoclonal antibody in 12 patients with moderate to severe atopic dermatitis. The authors observed rapid and sustained clinical benefit, with 83% achieving Eczema Area and Severity Index 50 (EASI50) and 33% EASI75. Also, they found significant reduction in peripheral eosinophils and skin neutrophil infiltration [73]. However, etokimab failed in phase 2b study in atopic dermatitis (NCT03533751). In a 6-week placebo-controlled phase 2a study, the researchers evaluated the safety and the ability of a single dose of etokimab to desensitize peanut-allergic adults. Participants received either etokimab ($n = 15$) or blinded placebo ($n = 5$). Efficacy measurements for etokimab vs. placebo participants at the day 15 and 45 food challenge demonstrated, respectively, 73% vs. 0% ($P = 0.008$) to 57% vs. 0% (ns), respectively (NCT02920021) [74•]. And a phase 2 clinical trial in CRS patients with nasal polyps is ongoing. Estimate completion date is by the end of 2020.

Conclusion

With the introduction and general acceptance of the unified airway concept, chronic rhinosinusitis and asthma were no longer treated as mutually exclusive diseases in the airway and require the concerted effort of both upper and lower airway clinicians to devise comprehensive treatments. Despite the introduction and successful application of biologics in treatment of chronic airway inflammatory diseases, their use for CRS with asthma has yet to become a mainstay treatment due to the lack of definitive evidence to guide treatment selection based on the available biologics. Large-scale randomized placebo-controlled clinical trials that can elucidate the therapeutic benefits of the biologics are still

required. Nevertheless, the availability of the biologics and their clinical efficacy has lent confidence to the overall management of CRS with asthma in order to reduce the socioeconomic burden of the diseases.

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Declarations

Conflict of Interest

Yingxiang Xu, Mingmin Bi, Kai Sen Tan, Jiaoping Mi, and Haiyu Hong declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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