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RHINITIS, CONJUNCTIVITIS, AND SINUSITIS (J OPPENHEIMER AND J CORREN, SECTION EDITORS)

Biologic Therapies for Allergic Rhinitis and Nasal Polyposis

Bob Geng[1] · Michelle Dilley[1] · Christine Anterasian[2]

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Abstract

Purpose of Review There is an emerging body of research on targeted biologic therapies for the treatment of severe inflammatory nasal disorders, especially chronic rhinosinusitis with nasal polyposis (CRSwNP). This paper will evaluate the efficacy of biologic therapies for severe nasal inflammation by summarizing key preclinical trials of biologics for animal models of allergic rhinitis and the recent phase 2 and 3 clinical trials of biologic therapies for CRSwNP.

Recent Findings Biologics that target the IL-4 receptor (dupilumab), IgE (omalizumab), and IL-5 (mepolizumab, reslizumab, and benralizumab) in patients with CRSwNP have shown improvement of various metrics including Sino-Nasal Outcome Test (SNOT-22) scores, Nasal Polyp Scores (NPS), Nasal Congestion Scores (NCS), and Lund-Mackay sinus opacification scores.

Summary The efficacy demonstrated through the dupilumab phase 3 trials (LIBERTY NP SINUS-24 and SINUS-52) led to approval of the first biologic for the treatment of CRSwNP. Phase 3 trials for omalizumab (POLYP 1 and 2) and mepolizumab (SYNAPSE study) and post hoc analyses of phase 3 asthma studies for reslizumab and benralizumab have also demonstrated positive results for the use of biologics for patients with CRSwNP. Future efficacy studies and risk/benefit and cost analyses of these biologics and other cytokine targets for allergic rhinitis with and without nasal polyposis need to be performed.

Keywords Biologics · Allergic rhinitis · Chronic rhinosinusitis with nasal polyposis · Dupilumab · Omalizumab · Mepolizumab

Introduction

The pathogenesis of allergic rhinitis (AR) involves the process of allergen sensitization, generation of allergen-specific IgE, recruitment of inflammatory cells, and the eventual activation/degranulation of mast cell mediators. It is postulated that environmental allergens upon contact with the nasal mucosa through direct proteinase activity or binding to Toll-like receptors induce the generation of epithelial derived cytokines (TSLP, IL-25, IL-33) that signal the activation of innate lymphoid cells [1, 2]. In turn, these innate lymphoid cells help generate the cytokine milieu (IL-4, IL-5, and IL-13) to induce the differentiation of TH2 lymphocytes. The allergens are also taken up by antigen-presenting cells (dendritic cells), which then present the antigen to TH2 cells. Through the creation of a TH2 cytokine milieu, there is induction of class switch recombination of B cells towards the production of IgE [1, 2]. Allergen-specific IgE then binds onto the surface receptors of mast cells and basophils, and upon re-exposure to allergen will lead to cross-linking triggering subsequent degranulation of inflammatory mediators (histamine, tryptase, prostaglandins, leukotrienes, etc.) responsible for the generation of nasal symptoms [1]. Secretion of additional TH2 cytokines (IL-5) as well as chemokines leads to the recruitment of inflammatory cells such as eosinophils that further contribute to the chronic inflammation in AR.

Numerous studies evaluating both baseline, in-season natural exposure and post-nasal challenge nasal secretions have demonstrated the elevation of TH2 cytokines [2, 3]. In contrast to mast cell mediators, it has been demonstrated that TH2

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✉ Bob Geng
bgeng@health.ucsd.edu

Michelle Dilley
mdilley@health.ucsd.edu

Christine Anterasian
canteras@uw.edu

[1] University of California San Diego and Rady Children's Hospital, San Diego, CA, USA

[2] University of Washington School of Medicine, Seattle, WA, USA

cytokine levels in the nasal secretion do not rise immediately upon allergen exposure, but rise hours later in the response [3]. Direct examination of nasal mucosal tissue demonstrated increased IL-4, IL-5, and IL-13 mRNA expression [2]. Conversely, various studies have found that TH1 cytokine profile is diminished in AR subjects in the absence of viral upper respiratory tract infection [2]. In fact, increased IL-4 to IFN-gamma ratio in nasal secretion has been strongly associated with the AR phenotype [4]. In vitro studies demonstrated that peripheral blood plasma cells and myeloid dendritic cells from AR subjects released a decreased amount of IL-12 and IFN-gamma [2, 5].

Recently, the roles of the TH17 family of cytokines have been examined in the pathogenesis of AR. IL-17 is thought to play a role in the inflammatory response in certain asthma phenotypes and chronic rhinosinusitis [2]. In AR, various studies demonstrate that elevations in IL-17 may be associated with dust-mite-related perennial disease, but the degree of its role in pathogenesis is yet to be completely elucidated [2].

Over the past several years, we have begun to better understand the interplay between the innate and adaptive immune responses. Epithelial-derived cytokines including TSLP and IL-33 are believed to play a crucial role in the signaling and response of the innate lymphoid cells that help initiate the eventual activation of the TH2 response [1, 2]. These cytokines have been shown to be relevant in the pathogenesis of asthma, but their roles in AR have not been clearly delineated. Small studies with human nasal specimens demonstrated elevated expression of TSLP in the nasal mucosa [2]. Further investigations are needed to demonstrate a definitive role for these epithelial-derived cytokines in AR.

Another related but distinct nasal pathology involving a TH2 cytokine pattern of inflammation is chronic rhinosinusitis with nasal polyposis (CRSwNP). CRSwNP is thought to be a distinct form of chronic sinus disease with a different mechanistic pathway than chronic rhinosinusitis without polyposis (CRSsNP). The exact pathophysiology of nasal polyposis is not completely elucidated, but studies have shown that it follows a predominantly TH2 pattern of inflammation [6]. Levels of IgE and IL-5 are both seen to be elevated in nasal polyp tissue. Eosinophilic inflammation and release of toxic mediators driven by an increased expression of IL-5 and eotaxin play a crucial role in the mechanism of the development of nasal polyps [6]. Inhibition of IL-5 has been examined in several clinical studies by anti-IL-5 monoclonal antibodies in an effort to diminish the eosinophilic activation with the hope of nasal polyp reduction [6, 7].

A significant amount of research has taken place investigating the efficacy of biologic therapies for severe asthma. Recently, there has been a growing amount of clinical studies evaluating the efficacy of biologic therapies for severe nasal inflammation. This review will attempt to provide a summary of key preclinical studies of biologic agents for animal models of allergic rhinitis and the more recent phase 2 and 3 clinical trials on CRSwNP (Table 1). These studies shed some light on the underlying immunologic mechanisms of allergic nasal disease and provide further directions for continued clinical investigation.

IL-13

IL-13 is one of the key TH2 cytokines mediating the allergic inflammatory response. IL-13 is found to be associated with mucous gland hyperplasia and stimulation of airway smooth muscle cells and in conjunction with IL-4 promotes c [8]. In a mouse model, IL-13 was shown to be essential in the late phase of AR [9]. Other mouse models demonstrated that exogenous airway administration of IL-13 led to increased eosinophilic inflammation and airway hyperresponsiveness with subsequent remodeling [10]. Mice that have knocked out IL-13 expression were also found to be resistant to airway hyperresponsiveness from allergen exposure [11]. These preclinical observations have led to significant clinical investigations into anti-IL-13 therapy in allergic asthma with positive results [12].

The initial clinical study on the efficacy of IL-13 for AR was done by Nicholson et al. in 2011. In that study, the investigators examined the effect of a single anti-IL-13 monoclonal antibody infusion (6 mg/kg of QAX576 by Novartis) on nasal lavage cytokine levels and nasal symptom score following direct nasal allergen challenge [8]. The study was a randomized placebo controlled trial with 16 subjects receiving the anti-IL-13 monoclonal antibody and 15 subjects receiving the placebo infusion. In addition, a third arm was also present with 5 subjects only receiving intranasal fluticasone propionate without any infusions to evaluate the effect of intranasal corticosteroid alone on post-nasal challenge endpoints.

A baseline nasal allergen challenge was performed at screening between 14 and 28 days prior to intervention [8]. Timothy grass pollen extract manufactured by ALK-Abello was used with the equivalent of 1 μg of *Phleum pratense* administered in 100 μL of fluid per nostril per challenge [3]. The endpoints that were evaluated were Total Nasal Symptom Score (TNSS) and nasal lavage differential leukocyte count as well as cytokine measurements (IL-4, IL-13, IL-5, and eotaxin) from a synthetic absorptive matrix nasosorption procedure [8]. Both the TNSS and the synthetic absorptive matrix procedure were obtained at baseline, 15 min, 30 min, and each hour up to 8 h post-challenge. Nasal lavage sampling was obtained at baseline, 30 min, and then every 2 h up to 6 h post-challenge. Following medication intervention, the same nasal challenge procedure was repeated on days 5, 6, and 7 of the study [8].

The authors found that the infusion of anti-IL-13 monoclonal antibody was associated with a significant reduction of

Table 1 Summary of clinical trials on biologics for chronic rhinosinusitis with nasal polyps (CRSwNP)

		Primary endpoints	Secondary endpoints
Dupilumab	Phase 2: Bachert et al. *JAMA*. 2016	NPS improved after 16 weeks (LS mean change − 1.6, $p < 0.001$)	Improved Lund-Mackay CT score (LS mean change − 8.8, $p < 0.001$), SNOT-22 (LS mean change − 18.1, $p < 0.001$), UPSIT score (LS mean change + 14.8, $p < 0.001$), peak nasal inspiratory flow (LS mean change + 33, p =0.002), and self-reported daily total symptom score (− 2.51, $p < 0.0001$). Decreased Th2 biomarker levels including TARC, eotaxin-3, and total IgE levels
	Phase 3: Bachert et al. LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52. *Lancet*. 2019	Improved NPS, NCS, Lund-Mackay CT score at 24 weeks (LS mean changes in SINUS-24/SINUS-52 respectively: − 2.06/− 1.80; − 0.89/− 0.87; − 7.44/− 5.13; all $p < 0.0001$)	Improved UPSIT, loss of smell score, SNOT-22, and total symptom score (LS mean changes in SINUS-24/SINUS-52 respectively: +10.56/+10.52; − 1.12/− 0.98; − 21.12/− 17.36; − 2.61/− 2.44; all $p < 0.0001$)
Omalizumab	Phase 2: Gevaert et al. *JACI*. 2013	NPS improved after 16 weeks (mean change − 2.67, $p = 0.001$)	Improved Lund-Mackay CT score, NCS, rhinorrhea, loss of sense of smell, wheezing, dyspnea, SF-36, and RSOM-31
	Phase 3: Gevaert et al. POLYP 1 and POLYP 2. *JACI*. 2020	Improved NPS and NCS at 24 weeks (mean changes in POYLP 1/POLYP 2 respectively: − 1.08, $p < 0.0001$/− 0.90, $p = 0.014$ and − 0.89, $p = 0.0004$/− 0.70, $p = 0.0017$)	Improved UPSIT, loss of smell score, SNOT-22, total symptom score (mean changes in POLYP 1/POLYP 2 respectively: +4.44, $p = 0.0024$/+4.31, $p = 0.0011$; − 0.56, $p = 0.0161$/− 0.58, $p = 0.0024$; − 24.7/− 21.59, both $p < 0.0001$; − 2.97, $p = 0.001$/− 2.53, $p < 0.0001$)
Reslizumab	Phase 2: Gevaert et al. *JACI*. 2006	NPS improved within 4 to 8 weeks, although the study was not sufficiently powered to determine significance	
	Post hoc analyses of phase 3 asthma studies: Weinstein et al. BREATH 1 and BREATH 2. *JACI*: In Practice. 2019	Asthma patients with CRSwNP had a larger reduction in frequency of asthma attacks compared to asthma patients without CRSwNP (reduction of 83% vs 44%)	
Mepolizumab	Phase 2: Gevaert et al. *JACI*. 2011	NPS improved at 8 weeks (mean change − 1.3, $p = 0.028$)	Improved Lund-Mackay CT score. Trends towards improvement in nasal symptom scores and nasal inspiratory peak flow measures
	Phase 2: Bachert et al. *JACI*. 2017	Decreased need for nasal surgery in patients treated with mepolizumab at 25 weeks (30% in the mepolizumab group no longer required surgery compared to 10% in placebo group)	Improved NPS, nasal polyposis severity VAS scores, and SNOT-22
	Phase 3: Hopkins et al. SYNAPSE study. *Eur Respir J*. 2020	NPS improved at 52 weeks (median change − 1 vs. 0; $p < 0.001$). Nasal obstruction VAS scores at weeks 49–52 improved (− 4.41 vs. − 0.82; $p < 0.001$)	Improved SNOT-22 (− 30 vs. − 14; $p = 0.003$), improved sinonasal symptoms via VAS scores (v4.48 vs. − 0.9; $p = 0.003$), reduced NP surgery (decrease by 57%), and reduced systemic corticosteroid treatment (decrease by 12%)
Benralizumab	Observation Study: Lombardo et al. *Int J Immunopathol Pharmacol*. 2020	SNOT-22 improved from 61.1 to 26.30 ($p < 0.001$), NRS decreased from 7.2 to 3.4 ($p < 0.001$), NPS decreased from 4.2 to 2.5 ($p < 0.001$), Lund-Mackay CT score decreased from 16.6 to 6.9 ($p < 0.001$), and peripheral blood eosinophils decreased from 807.3 to 0 cells/μL ($p < 0.0001$)	
	Post hoc analyses of phase 3 asthma studies: Maspero et al. SIROCCO and CALIMA trial. *JACI*. 2018	Larger reduction of asthma exacerbations in patients with nasal polyps treated with benralizumab (54% reduction in subgroup with nasal polyps vs 42% reduction in all patients)	

Table 1 (continued)

	Primary endpoints	Secondary endpoints
Post hoc analyses of phase 3 asthma studies: Harrison et al. ANDHI Trial. *ATS International Conference*. 2020	SNOT-22 improved at week 4 (LS mean change − 7.47, $p = 0.0105$) and at week 24 (LS mean change − 8.91, $p = 0.0204$)	

NPS Nasal Polyp Score (0–8 scale), *LS* least squares, Lund-Mackay score (sinus opacification, 0–24 scale), *SNOT-22 score* Sino-Nasal Outcome Test score (0–110 scale), *UPSIT score* University of Pennsylvania Smell Identification Test score (0–40 scale), *TARC* thymus and activation-regulated chemokine, *NCS* nasal congestion or obstruction score (0–3 scale), Loss of smell score (0–3 scale), Total symptom score (0–9 scale), *SF-36* Short-Form Health Questionnaire, *RSOM-31* 31-item Rhinosinusitis Outcome Measuring Instrument, nasal polyposis severity visual analog scale (VAS) score (0–10 scale), *NRS* numerical rating scale (0–10 scale)

mucosal fluid IL-13 level following allergen challenge compared to placebo [8]. There was no appreciable difference in IL-5 levels between the treatment and placebo groups post-challenge, but the intranasal fluticasone arm demonstrated a significant decrease in IL-5 level [8]. Eosinophil count in nasal lavage did not show appreciable reduction with anti-IL-13 treatment [8]. The TNSS did not demonstrate any significant change compared to the placebo group. During post hoc analysis when the authors stratified based on pre-treatment IL-13 level post-challenge, they found that, among subjects in the treatment group, those who had high IL-13 levels (only 4 subjects) trended towards a reduction in symptom score during post-treatment challenges [8]. However, the sample size was too small to make any definitive conclusions.

IL-4 and IL-13

The quintessential cytokine responsible for class switch recombination to IgE production for the B cell is IL-4 [13]. Along with IL-13, it plays a significant role in shifting the immune response towards a TH2 pathway of inflammation [14]. The receptors for IL-4 and IL-13 share the alpha-subunit of the IL-4 receptor [15]. Dupilumab is an inhibitor of the alpha-subunit of the IL-4 receptor, which can theoretically inhibit the signaling of both the IL-4 and IL-13 receptors [14]. Dupilumab has been extensively studied in eosinophilic asthma, but its direct impact on allergic rhinitis has not been thoroughly evaluated. However, in one of the studies on its effect on asthma, the 22 Sino-Nasal Symptom Outcome Test (SNOT-22) was measured as a secondary endpoint, which shed some light on the effect of dual IL-4/IL-13 blockade on allergic nasal inflammation [14]. The SNOT-22 ranged from 0 to 110 points with higher values indicating more severe sinonasal symptoms.

In the study of dupilumab on persistent asthma with elevated eosinophil levels by Wenzel et al., 52 subjects were randomized to the treatment group and 52 to the placebo group [14]. Subjects were all chosen based on history of persistent asthma as well as peripheral blood eosinophilia and/or elevated sputum eosinophil levels. These subjects were given either weekly dupilumab or placebo injections for 12 weeks. The primary endpoint of the study was asthma exacerbation. The analysis of covariance was used as the statistical method of comparing the change from baseline of the SNOT-22 between the treatment and placebo groups. In the dupilumab group, there was a statistically significant decrease of 8.26 (± 2.20) vs. an increase of 0.23 (± 2.15) in the placebo group [14]. A difference of at least 8.9 points was used by the authors as the minimum criteria for achieving clinical significance [14]. Assessing each of the 22 categories of symptoms separately by the survey, 10 categories achieved statistical significance favoring the treatment group

vs. the placebo group: need to blow nose, nasal blockage, cough, post-nasal discharge, thick nasal discharge, ear fullness, ear pain, decreased sense of smell/taste, lack of a good night's sleep, and frustration/irritability secondary to nasal symptoms [14]. While the difference in SNOT-22 between the placebo and the treatment group was deemed to be statistically significant, the authors did not interpret it as being clinically significant because the difference between the two groups (8.49) did not reach the 8.9-point minimum threshold of clinical significance [14]. However, the study suggested that the drug may hold promise for patients with severe allergic rhinitis.

Dupilumab subsequently entered clinical trials for patients with chronic sinusitis with nasal polyposis. In a double-blind placebo-controlled proof-of-concept phase 2a study [16], 60 adult nasal polyposis patients refractory to intranasal corticosteroids were randomly assigned to 16 weeks of 300 mg dupilumab (n = 30) or placebo (n = 30) on a mometasone furoate nasal spray background. The primary endpoint of the study was change in endoscopic nasal polyp score (NPS) for patients on dupilumab compared to placebo after 16 weeks of treatment, which was significantly improved in patients on dupilumab (least squares (LS) mean change − 1.6, $p < 0.001$) [16]. Dupilumab also compared favorably to placebo with regard to the secondary endpoints of Lund-Mackay CT score (LS mean change − 8.8, $p < 0.001$) to evaluate nostril patency, SNOT-22 score (LS mean change − 18.1, $p < 0.001$) to evaluate quality of life (including significant improvement in number of sick days and productivity), University of Pennsylvania Smell Identification Test (UPSIT) score (LS mean change + 14.8, $p < 0.001$) to evaluate sense of smell, and morning peak nasal inspiratory flow (LS mean change + 33, $p = 0.002$). At 16 weeks, dupilumab showed significant and clinical meaningful improvement (calculated using Cohen's rule) in self-reported daily total symptom score (− 2.51, $p < 0.0001$) compared to placebo with significant changes seen in all 3 sub-categories of nasal congestion/obstruction, decreased smell, and anterior/posterior rhinorrhea (all $p < 0.001$) [16]. In addition, Th2 biomarker levels in peripheral blood (all patients), nasal secretions (all patients), and nasal polyp biopsies (15/60 patients) were compared between baseline and 12–16 weeks after the initiation of treatment. Statistically lower levels of TARC (peripheral blood $p < 0.0001$), eotaxin-3 (plasma $p < 0.0001$, nasal secretions $p < 0.001$, nasal polyp biopsies $p = 0.031$), and total IgE (plasma $p < 0.001$, nasal secretions $p = 0.022$, nasal polyp biopsies $p = 0.047$) were seen in patients after treatment with dupilumab but no changes were seen in patients on placebo [16–18]. In addition, significantly lower ECP levels ($p = 0.008$) were seen in nasal polyp biopsies, but not observed in peripheral blood or nasal secretions [16, 18]. Further testing on nasal polyp biopsies revealed lower eotaxin-3 ($p = 0.008$) and TARC ($p = 0.016$) levels compared with baseline for patients on dupilumab with no significant changes seen in patients receiving placebo [17]. Mean blood eosinophil count was unchanged after 16 weeks of treatment [16]. Dupilumab was well tolerated with injection site reactions, headache, and nasopharyngitis being the most frequently reported adverse events [16]. This study suggests that patients with nasal polyposis on chronic nasal steroid therapy will have clinically significant improvement in symptoms and disease severity with dupilumab add-on therapy compared to placebo.

Dupilumab more recently completed phase 3 trials, LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52, for the treatment of severe CRSwNP [19••]. Adult patients with CRSwNP and symptoms despite intranasal corticosteroid therapy, systemic corticosteroid use in the preceding 2 years, or prior sinonasal surgery were included [19••]. Patients in SINUS-24 were randomly assigned to subcutaneous dupilumab (n = 143) or placebo (n = 133) every 2 weeks for 24 weeks. Those in SINUS-52 were randomly assigned to dupilumab every 2 weeks for 52 weeks (n = 150), dupilumab every 2 weeks for 24 weeks and then every 4 weeks for 28 weeks (n = 145), or placebo every 2 weeks for 52 weeks (n = 153) [19••]. All groups were also on intranasal mometasone. Patients treated with dupilumab had statistically significant reduced polyp size at 24 weeks with LS mean differences between dupilumab and placebo groups in NPS decreased by 2.06 ($p < 0.0001$) in SINUS-24 and decreased by 1.80 ($p < 0.0001$) in SINUS-52 [19••]. Nasal congestion and obstruction also improved in the dupilumab groups with LS mean differences in the Nasal Congestion Score (NCS) decreased by 0.89 ($p < 0.0001$) in SINUS-24 and decreased by 0.87 ($p < 0.0001$) in SINUS-52 [19••]. Additionally, radiographic sinus opacification improved compared to placebo with LS mean differences in Lund-Mackay CT scores decreased by 7.44 ($p < 0.0001$) in SINUS-24 and decreased by 5.13 ($p < 0.0001$) in SINUS-52 [19••]. Other measures demonstrated improvement in UPSIT, loss of smell score, SNOT-22, and total symptom score [19••]. Patients on dupilumab had improved smell as measured by UPSIT in SINUS-24 (LS mean change + 10.56, $p < 0.0001$) and in SINUS-52 (LS mean change + 10.52, $p < 0.0001$) as well as improved loss of smell score in SINUS-24 (LS mean change − 1.12, $p < 0.0001$) and in SINUS-52 (LS mean change − 0.98, $p < 0.0001$) [19••]. Patients also had improved SNOT-22 in SINUS-24 (LS mean change − 21.12, $p < 0.0001$) and in SINUS-52 (LS mean change − 17.36, $p < 0.0001$) as well as improved total symptom score in SINUS-24 (LS mean change − 2.61, $p < 0.0001$) and in SINUS-52 (LS mean change − 2.44, $p < 0.0001$) [19••]. The rates of adverse events were generally similar between the dupilumab and placebo groups [19••]. The efficacy and safety demonstrated through these phase 3 trials led to the approval of dupilumab as the first biologic for the treatment of CRSwNP.

Anti-IgE

The anti-IgE monoclonal antibody omalizumab has already been approved for the treatment of refractory allergic asthma and more recent studies have analyzed the role of omalizumab in patients with CRSwNP. Omalizumab binds circulating IgE, inhibits binding to the IgE receptor, and decreases IgE receptors on mast cells, basophils, and dendritic cells [20]. Omalizumab was studied in a randomized trial of 24 patients with CRSwNP and comorbid asthma. Based on total serum IgE levels and body weight, patients received 4 to 8 subcutaneous doses of omalizumab ($n = 16$) or placebo ($n = 8$) [20]. In the omalizumab-treated group, there was a significant decrease in total nasal endoscopic polyp score after 16 weeks (− 2.67, $p = 0.001$) compared to placebo (− 0.12, $p = 0.99$) [20]. The omalizumab-treated group also had statistically significant improvements in Lund-Mackay CT score, NCS, rhinorrhea, loss of sense of smell, wheezing, dyspnea, Short-Form Health Questionnaire (SF-36), and on the 31-item Rhinosinusitis Outcome Measuring Instrument (RSOM-31) [20].

Omalizumab has also shown positive results for patients with inadequately controlled CRSwNP despite intranasal corticosteroids in 2 replicated phase 3 trials, POLYP 1 and POLYP 2 [21••]. Adult patients met inclusion criteria if they had persistent bilateral nasal polyps with an endoscopic NPS ≥ 5, nasal congestion, and impaired health-related quality of life (HRQoL) with SNOT-22 score ≥ 20 despite intranasal corticosteroid therapy. Patients were also required to have an elevated serum IgE level from 30 to 1500 IU/mL [21••]. If patients had other sinonasal or pulmonary disorders, aside from asthma, they were excluded [21••]. Patients were randomized to subcutaneous omalizumab or placebo for 24 weeks. Both groups were also on intranasal mometasone for the duration of the study [21••]. In POLYP 1 ($n = 138$), 69 of 72 treated with omalizumab and 64 of 66 in the placebo group completed the study. In POLYP 2 ($n = 127$), 58 of 62 treated with omalizumab and 63 of 65 in the placebo group completed the study [21••]. As early as the first post-treatment assessment at week 4, patients treated with omalizumab had greater improvement in NPS, NCS, and SNOT-22 score [21••]. At week 24, the mean changes from baseline in the omalizumab group vs. the placebo group for NPS was decreased by 1.08 vs. increased by 0.06 ($p < 0.0001$) in POLYP 1 and decreased by 0.90 vs. decreased by 0.31 ($p = 0.0140$) in POLYP 2 and for NCS was decreased by 0.89 vs. decreased by 0.35 ($p = 0.0004$) in POLYP 1 and decreased by 0.70 vs. decreased by 0.20 ($p = 0.0017$) in POLYP 2. Patients treated with omalizumab compared to placebo at 24 weeks also had statistically significant improvement in secondary endpoints including UPSIT, loss of smell score, SNOT-22 score, and total symptom score (mean changes in POLYP 1/POLYP 2 respectively: + 4.44, $p = 0.0024$/+ 4.31, $p = 0.0011$; − 0.56, $p = 0.0161$/− 0.58, $p = 0.0024$; − 24.7/− 21.59, both $p < 0.0001$; − 2.97, $p = 0.001$/− 2.53, $p < 0.0001$) [21••]. During the study, rescue systemic corticosteroid treatment was required more frequently in the placebo-treated patients (6.2% of POLYP 1 and 2 combined) vs. the omalizumab-treated patients (2.3% of POLYP 1 and 2 combined) [21••]. Also, a reduced need for surgery by week 24 was seen more frequently in omalizumab-treated patients (reduction of 18.8% from POLYP 1 and 16.9% from POLYP 2) vs. the placebo-treated patients (reduction of 3.1% from POLYP 1 and 3.2% from POLYP 2) [21••]. Adverse events were similar between omalizumab and placebo groups with no reported omalizumab-associated risks [21••]. These phase 3 trials demonstrate safety and efficacy for using omalizumab in adult patients with severe CRSwNP.

IL-5

Eosinophils play a significant role in the development of allergic disorders. IL-5 is a potent stimulator of eosinophilic growth and proliferation, thus making it a natural target for therapeutic intervention in allergic diseases [22]. It is produced by TH2 lymphocytes, eosinophils, basophils, and natural killer T cells [23]. IL-5 promotes eosinophilic activation through several mechanisms: augmenting bone marrow eosinophil differentiation and maturation, increasing migration of eosinophils to target tissues, and inhibiting apoptosis of eosinophils [23]. Studies evaluating the efficacy of anti-IL-5 monoclonal antibodies for allergic rhinitis in mouse models showed conflicting results. One study by Asakura et al. showed that anti-IL-5 monoclonal antibody inhibited early-phase symptoms and late-phase eosinophilia in mice [24]. However, in a study by Saito et al. that examined an experimental model of allergic rhinitis in IL-5-deficient mice vs. wild type, the authors found that IL-5 suppression did not lead to resolution of allergic rhinitis symptoms or nasal histamine hyperresponsiveness [25]. The clinical studies evaluating its efficacy in nasal disease are still limited to mainly the treatment of nasal polyposis. There is a higher concentration of IL-5 as well as higher level of IL-5 mRNA expression in nasal polyp tissue [23].

The first clinical anti-IL-5 study for nasal polyposis was the single-dose randomized placebo-controlled double-blind study on reslizumab for the treatment of severe and/or recurrent nasal polyposis [7]. Of 24 subjects, 8 received placebo, 8 received the lower dose of reslizumab (1 mg/kg), and 8 received the higher dose (3 mg/kg) [7]. Intervention drug was administered by a 30-min intravenous infusion. Both clinical endpoints (NPS, symptom score, and nasal peak inspiratory flow) and biomarker measurements (peripheral eosinophilia, peripheral and nasal secretion levels of IL-5 and various other cytokines) were evaluated in the study [7]. Following intervention, 5 of 8

subjects in the 1 mg/kg reslizumab group showed improvement in NPS up to 12 weeks post-infusion, 4 of 8 subjects in the 3 mg/kg group showed improvement in polyp score up to 4 weeks post-infusion, and only 1 of 8 subjects in the placebo group showed improvement in score [7]. Four of 8 subjects in the 3 mg/kg group showed worsening of score at 12 weeks [7]. Symptom score and nasal peak inspiratory flow did not improve compared to placebo, but the authors stated that the study was not powered sufficiently to detect significant changes in those parameters [7]. In terms of biomarker changes, there was a significant reduction in peripheral blood eosinophilia and decrease in nasal fluid IL-5 concentration in treatment groups vs. placebo [7].

From 2 phase 3 trials on reslizumab and asthma outcomes (BREATH 1 and 2), Weinstein et al. conducted a post hoc analysis examining a subgroup of eosinophilic asthma patients with self-reported CRSwNP [26•]. Asthma patients with CRSwNP had a larger reduction in frequency of asthma attacks compared to asthma patients without CRSwNP (reduction of 83% vs 44%) [26•]. Lung function as measured by FEV1 was also significantly improved in patients with CRSwNP treated with reslizumab compared with placebo [26•].

Other clinical studies have examined the efficacy of another anti-IL-5 monoclonal antibody, mepolizumab, on nasal polyposis. Gevaert el al. analyzed 20 patients receiving 2 doses of 750 mg of mepolizumab intravenous injections 4 weeks apart vs. 10 patients receiving 2 doses of placebo intravenous injections in a randomized double-blind placebo-controlled study [6]. Clinical and biomarker endpoints were compared between 8 weeks and at baseline. Clinical outcome measures included nasal polyposis score, sinus CT scan score, and nasal symptom score as well as nasal inspiratory peak flow measurements. Biomarker measurements included peripheral blood eosinophilia and various cytokine measurements in the blood and nasal secretion. Overall, there was no statistically significant difference in rate of adverse events between treatment and placebo groups [6]. The study achieved a significant reduction in the mean total polyp score in the treatment vs. placebo group (mean change − 1.3, $p = 0.028$) [6]. Twelve of 20 subjects in the treatment group experienced some type of reduction in total polyp score compared to only 1 of 10 subjects in the placebo group [6]. Ten of 20 subjects in the treatment group demonstrated an improvement on CT scan vs. only 2 of 10 subjects in the placebo group [6]. Again, the nasal symptom scores and the nasal inspiratory peak flow measures trended towards improvement in the treatment group but did not reach statistical significance [6]. In terms of biomarkers, peripheral blood eosinophilia as well as serum ECP and serum IL-5 receptor alpha levels demonstrated significant decrease in the treatment vs. placebo groups [6]. However, there was no significant difference in nasal ECP, nasal IL-5, and nasal total IgE levels between the two groups [6].

A subsequent randomized trial assessed whether mepolizumab reduced the need for sinus surgery in patients with severe nasal polyposis [27•]. Patients received mepolizumab ($n = 54$) or placebo ($n = 51$) every 4 weeks for a total of 6 doses [27•]. After 25 weeks of treatment, 30% of patients in the mepolizumab group no longer required surgery compared to 10% in the placebo group [27•]. The mepolizumab group had statistically significant improvements in NPS, nasal polyposis severity VAS scores, and SNOT-22 scores [27•].

More recently, the phase 3 SYNAPSE study evaluated subcutaneous mepolizumab in adult patients with severe CRSwNP and found decreased nasal polyp size and obstruction over 52 weeks [28••]. Patients were included if they had a prior nasal polyp surgery and were in need of further surgery due to increased polyp size with endoscopic NPS ≥ 5 and severe symptoms with an overall visual analog scale (VAS) symptom score > 7 despite intranasal corticosteroid therapy [28••]. Patients were randomized to subcutaneous mepolizumab ($n = 206$) or placebo ($n = 201$) for 52 weeks with both groups also on intranasal mometasone [28••]. At 52 weeks, those treated with mepolizumab demonstrated a statistically significant improvement in median endoscopic NPS vs. placebo (− 1 vs. 0; $p < 0.001$) [28••]. The median nasal obstruction VAS scores at weeks 49–52 also significantly decreased for those on mepolizumab vs. placebo (− 4.41 vs. − 0.82; $p < 0.001$) [28••]. During the study, fewer patients on mepolizumab required rescue systemic corticosteroid treatment, 25% compared to 37% on placebo [28••]. Also during the 52 weeks, there was a 57% lower risk and longer time to first nasal surgery in patients treated with mepolizumab [28••]. Patients treated with mepolizumab vs. placebo also demonstrated improvement in sinonasal symptoms via VAS scores (− 4.48 vs. − 0.9; $p = 0.003$) and HRQoL via SNOT-22 (− 30 vs. − 14; $p = 0.003$) [28••]. Adverse events were similar between mepolizumab and placebo groups [28••].

Benralizumab is another anti-IL-5 agent currently under investigation for CRSwNP. Small studies to date have analyzed the effects of benralizumab in patients with concomitant asthma and nasal polyps. The observational study by Lombardo et al. assessed the effects of benralizumab in 10 patients with allergic CRSwNP and severe eosinophilic asthma [29]. SNOT-22 score, numerical rating scale (NRS), NPS, Lund-Mackay CT score, and peripheral blood eosinophils were measured at baseline and after 24 weeks of treatment with benralizumab [29]. All endpoints demonstrated significant improvement. SNOT-22 improved from 61.1 to 26.30 ($p < 0.001$), NRS decreased from 7.2 to 3.4 ($p < 0.001$), NPS decreased from 4.2 to 2.5 ($p <$

0.001), Lund-Mackay CT score decreased from 16.6 to 6.9 ($p < 0.001$), and peripheral blood eosinophils decreased from 807.3 to 0 cells/μL ($p < 0.0001$) [29]. The phase 3 trials SIROCCO and CALIMA investigating benralizumab treatment of severe asthma underwent pooled subgroup analysis for those with nasal polyps [30•]. Benralizumab reduced asthma exacerbation rates by 42% for all patients and post hoc analysis showed a 54% reduction in asthma exacerbation rates in patients with nasal polyps [30•]. This suggests that the presence of nasal polyps may enhance the efficacy of benralizumab treatment of severe asthma [30•]. Another phase 3b trial, the ANDHI trial, investigating benralizumab for severe eosinophilic asthma, performed post hoc analyses on SNOT-22 in those with comorbid nasal polyps [31•]. The NP sub-study population consisted of 153 patients with clinician-diagnosed NP (23.3% of the total population with severe eosinophilic asthma) [31•]. Improvement in SNOT-22 was seen from week 4 and maintained at week 24 for those treated with benralizumab (LS mean change at week 4 − 7.47, $p = 0.0105$; at week 24 − 8.91, $p = 0.0204$) [31•]. There are other ongoing randomized control trials for the evaluation of benralizumab in patients with CRSwNP (National Library of Medicine, NCT03450083 and NCT03401229). Overall, many of these anti-IL-5 monoclonal antibody studies in nasal polyposis have showed positive findings.

Other Cytokine Targets

In addition to the classic TH2 cytokines, other cytokine targets have been explored in animal models for therapeutic intervention in atopic nasal disorders. Investigators have examined the potential of blocking cytokines in the TH17 pathway due to its involvement in mucosal immunity. IL-17 is the main TH17 cytokine and IL-23 is crucial in promoting and directing the differentiation of T-helper cells down the TH17 pathway [32]. Wang et al. examined the effect of blocking both IL-17 and IL-23 in a murine model of allergic rhinitis [22]. Both monoclonal antibodies were administered via intranasal route to ovalbumin-induced allergic rhinitis mice [33]. The authors found that IL-17 inhibition only led to a reduction of the TH2 inflammatory cellular response [33]. IL-23 inhibition led to symptom improvement (decreased nasal rubbing and sneezing) as well as allergic biomarker and cellular infiltrate reductions [33].

A more recently recognized cytokine involved in promoting the process of TH2 differentiation is IL-33 [34]. IL-33 is a key inflammatory cytokine that mediates eosinophilic infiltration. Kim et al. conducted a study examining the effect of anti-IL-33 monoclonal antibody on a murine model of allergic rhinitis. The authors injected the anti-IL-33 antibody into ovalbumin-induced allergic mice [34]. Compared to groups of mice that did not receive the treatment, they found decreased nose scratching and skin denudation, decreased total serum IgE level, and decreased eosinophilic infiltration in the nasal mucosa as well as decreased IL-4, IL-5, and IL-13 in the bronchoalveolar lavage fluid [34]. A more recent clinical study on IL-33 did not show significant differences between patients with eosinophilic CRSwNP ($n = 25$) vs. patients with noneosinophilic CRSwNP ($n = 27$) with respect to SNOT-22, VAS score, NPS, or CT score [35]. Additionally, the ECLIPSE phase 2 trial of IL-33 in patients with CRSwNP failed to achieve statistically significant improvement in NPS and SNOT-22 vs placebo at the week-8 interim analysis [36].

Conclusion

Due to our better understanding of the basic immunologic mechanisms underlying allergic diseases and the proliferation of trials of biologic agents for severe asthma, we will begin to see more targeted biologic therapies emerge for the treatment of severe inflammatory nasal disorders. Many of the agents that have been approved or are in clinical trials for severe asthma may also be efficacious for severe chronic rhinosinusitis, as we have seen already in the aforementioned studies. Currently, the role of biologics in patients with allergic rhinitis and nasal polyposis is not well defined and studies have been limited to patients with severe refractory CRSwNP. Efficacy of biologics in allergic rhinitis and chronic rhinosinusitis without nasal polyposis is theoretically plausible but no efficacy studies have yet to be performed. Biologics that target the IL-4 receptor (the receptor for IL-4 and IL-13), IgE, and IL-5 have all demonstrated efficacy in the treatment of CRSwNP. Other pathways beyond the conventional TH2 cytokines should be further explored. However, the high cost of these newer biologic agents may become an impediment towards their widespread use, and a clear cost and benefit determination would have to be considered.

Declarations

Conflict of Interest Author BG has the following disclosures relevant to this manuscript: speaking honoraria from GSK, Sanofi, Regeneron, and OptiNose as well as consulting fees from Regeneron and Astra-Zeneca; Research Support from Genentech.

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