



Therapeutic Antibodies for Nasal Polyposis Treatment: Where Are We Headed?

Aarti Agarwal¹ · Derek Spath¹ · David A. Sherris¹ · Hirohito Kita² · Jens U. Ponikau¹

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Abstract

This review article aims to outline what is known in the pathophysiology of chronic rhinosinusitis with nasal polyposis (CRSwNP) and describe the mechanism of the biologic agents being investigated for this disease. Chronic rhinosinusitis with nasal polyposis is an inflammatory disease of the nasal and paranasal mucosa, which causes symptoms of nasal obstruction, hyposmia, and rhinorrhea. Conventional therapy for CRSwNP includes intranasal corticosteroids (INCS) and polypectomy, but INCS offer only modest benefits, and recurrence after surgery is common. Therefore, effective pharmacologic therapies for CRSwNP are being actively sought. Monoclonal antibodies have been successful in other chronic diseases involving eosinophilic inflammation, such as chronic urticaria and asthma. Thus, researchers have begun expanding their scope and investigating the efficacy of these drugs in the treatment of nasal polyposis. The monoclonal antibodies under investigation (omalizumab (anti IgE), dupilumab (anti IL-4/IL-13), and reslizumab and mepolizumab (both anti IL-5), benralizumab (anti IL-5R α), and etokimab (anti IL-33)) target key players in the pathophysiology of nasal polyposis (NP). Dupilumab has just completed phase III trials for CRSwNP with positive results, while omalizumab, mepolizumab, and benralizumab are currently in phase III trials for this indication. At this time, while there are no FDA-approved biologics for use in NP, research has highlighted the contributions of IL-4, IL-5, IL-13, and IgE as disease mediators in the pathogenesis of NP. The current FDA-approved treatment of intranasal steroids does not provide significant relief for many patients; therefore, these phase III trials of monoclonal antibodies bring hope for an exciting new treatment option.

Keywords Nasal polyposis · Chronic sinusitis with nasal polyposis · Biologics · Monoclonal antibodies

Introduction

Nasal polyposis (NP) is a benign protruding of inflammatory nasal and paranasal mucosa (Fig. 1) in the background setting of chronic rhinosinusitis (CRSwNP). The disease must be differentiated from a nasal choanal polyp, an inverting papilloma, or cystic fibrosis, which can all mimic NP clinically. NP can be accompanied by mucociliary impairment, bacterial infection, or allergy and remains difficult to treat. In the general population, the prevalence of NP is 4% [1]. The chronic nature

of the disease lends itself to sino-nasal symptoms, which can be characterized by nasal obstruction, hyposmia, rhinorrhea, facial pressure, and postnasal drainage, all of which reduce the patient's quality of life significantly. Due to its overlap with other diseases with similar symptoms, nasal polyposis cannot be diagnosed by symptomatology alone and direct visualization guides diagnosis. Nasal endoscopy is used to visualize nasal polyps and is later used to monitor disease progression and treatment efficacy [2].

While the exact pathogenesis of nasal polyposis is not known, the presence of eosinophils appears to be a key denominator. Some research studies have attempted to classify nasal polyposis based on the intensity of eosinophilia, varying between different subgroups of patients, where patients with concomitant allergy or asthma tend to have the most intense eosinophilic inflammation [3]. Patients with a more severe eosinophilic inflammation display a type 2 (Th2) inflammatory pattern with increased expression of interleukins-4, -5, and -13 (IL-4, IL-5, IL-13) and sometimes increased concentrations of immunoglobulin E (IgE) [4]. In these patients, eosinophils

✉ Jens U. Ponikau
jponikau@buffalo.edu

¹ Department of Otolaryngology, Jacobs School of Medicine and Biomedical Sciences, Gromo Institute and Sinus Center, University at Buffalo, The State University of New York, 1237 Delaware Avenue, Buffalo, NY 14209, USA

² Department of Medicine, Division of Allergic Disease, Mayo College of Medicine, Mayo Clinic, Rochester, MN, USA

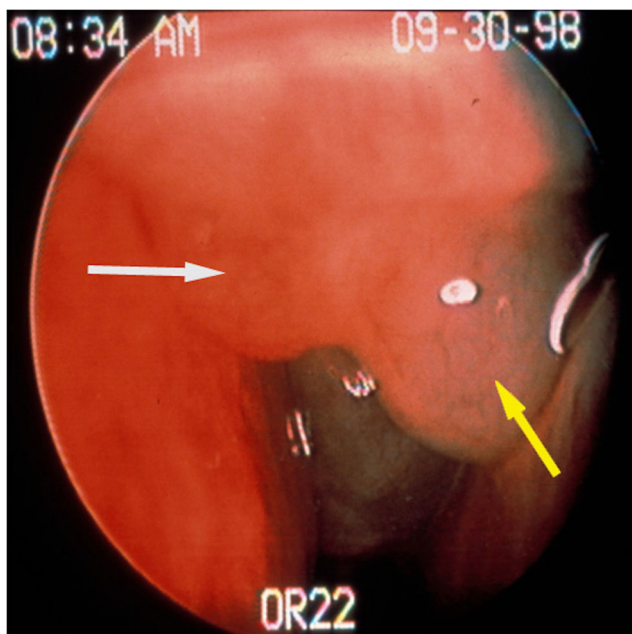


Fig. 1 Intranasal view of nasal polyposis (ethmoid area) showing chronic rhinosinusitis (CRS) with inflammatory mucosal thickening (white arrow) and nasal polyps (yellow arrow) protruding out of the chronic-inflamed mucosa

contribute to mucosal swelling and epithelial damage through the release of vasoactive substances and eosinophilic granular toxins. The abundance of eosinophils and their increased activation status in NP can be in part attributed to the combined pressures of increased hematopoiesis, a prolonged survival of eosinophils in the blood and tissue, and increased migration of eosinophils from the vasculature into the tissue [5].

Pathophysiology

Currently, both an allergic (IgE-mediated) and non-allergic pathway are understood in the pathophysiology of the underlying eosinophilia. Inhaled environmental allergens stimulate an immunologic response where especially IL-4 but also IL-13 can stimulate the initial differentiation of Th0 (naïve undifferentiated) cells to Th2 cells, a process commonly referred to as Th2 shifting [6]. IL-4 and IL-13 (which share the same receptor) are also required in inducing the expression of the vascular cell adhesion molecule 1 (VCAM-1), which is necessary for the adhesion of eosinophils on the endothelium of blood vessels. Eosinophils, in contrast to other white blood cells, express the VLA-4 receptor which facilitates binding to VCAM-1, allowing selective adhesion and migration of eosinophils from the vasculature to the nasal and sinus tissue [7].

Allergic and non-allergic phenotypes exist in CRS patients with or without gross nasal polyps. Non-allergic patients appear to have IL-13 in the nasal tissue, whereas allergic patients have both IL-4 and IL-13. In the non-allergic mechanism, IL-

13 from Th2 cells directly induces VCAM-1 expression and eosinophil recruitment. In the allergic model, Th2 cells release not only IL-13 but also IL-4, which also contributes to B cell differentiation into IgE-producing plasma cells (Fig. 2) [8]. With further exposure of the immune system to allergens, specific IgE antibodies are cross-linked on the surface of mast cells. This induces mast cell degranulation and release of pre-formed mediators, including IL-4, which furthers eosinophil recruitment. In addition, another cytokine from Th2 cells, IL-5, plays a key role in stimulating eosinopoiesis, differentiation, chemotaxis, and prolonged eosinophil survival by preventing apoptosis [9].

The eosinophilic inflammation causes edema due to increased vascular permeability, and the toxic eosinophil proteins, once released, induce mucus hypersecretion, impaired ciliary function and epithelial erosion. This eosinophil-mediated tissue damage potentiates the cycle of inflammation in the nasal mucosa, setting the stage for polyp formation [10, 11].

Current Management

Intranasal corticosteroids are the only FDA-approved treatment for nasal polyposis [12, 13]. Glucocorticoids can be effective in the treatment of nasal polyps due to their ability to reduce airway eosinophilia by preventing their migration, activation, and viability at the gene transcription and post-translational level [14]. This is achieved by reducing the expression of IL-4, IL-5, and IL-13. However, swollen polypoid nasal and sinus tissue, thick mucus, and impaired cilia activity reduce or prevent intranasal delivery.

Systemic glucocorticoids, while very effective, given over an extended period of time can cause significant side effects through immune and adrenal gland suppression, which results in an iatrogenic Cushing's syndrome. Features of Cushing's syndrome include osteoporosis, electrolyte imbalance, metabolic syndrome, and cardiac arrhythmias [15]. For patients with persistent symptoms despite medical management, surgical excision of polyps is considered. However, surgery does not treat the underlying cause of disease and recurrence of polyps is common. A prospective study completed with 363 patients having undergone endoscopic sinus surgery plus continued medical management for nasal polyposis showed that approximately 40% of patients had recurrence of nasal polyps [16]. Despite current medical or surgical approaches, many patients with nasal polyposis continue to have symptoms, significantly impairing their quality of life. Therefore, novel treatments that more specifically target disease and improve patient outcomes without causing systemic side effects are of utmost importance.

Patients with CRSwNP experience symptoms such as nasal blockage/obstruction, nasal discharge (anterior or posterior nasal drip), facial pain pressure, or reduction of sense of smell.

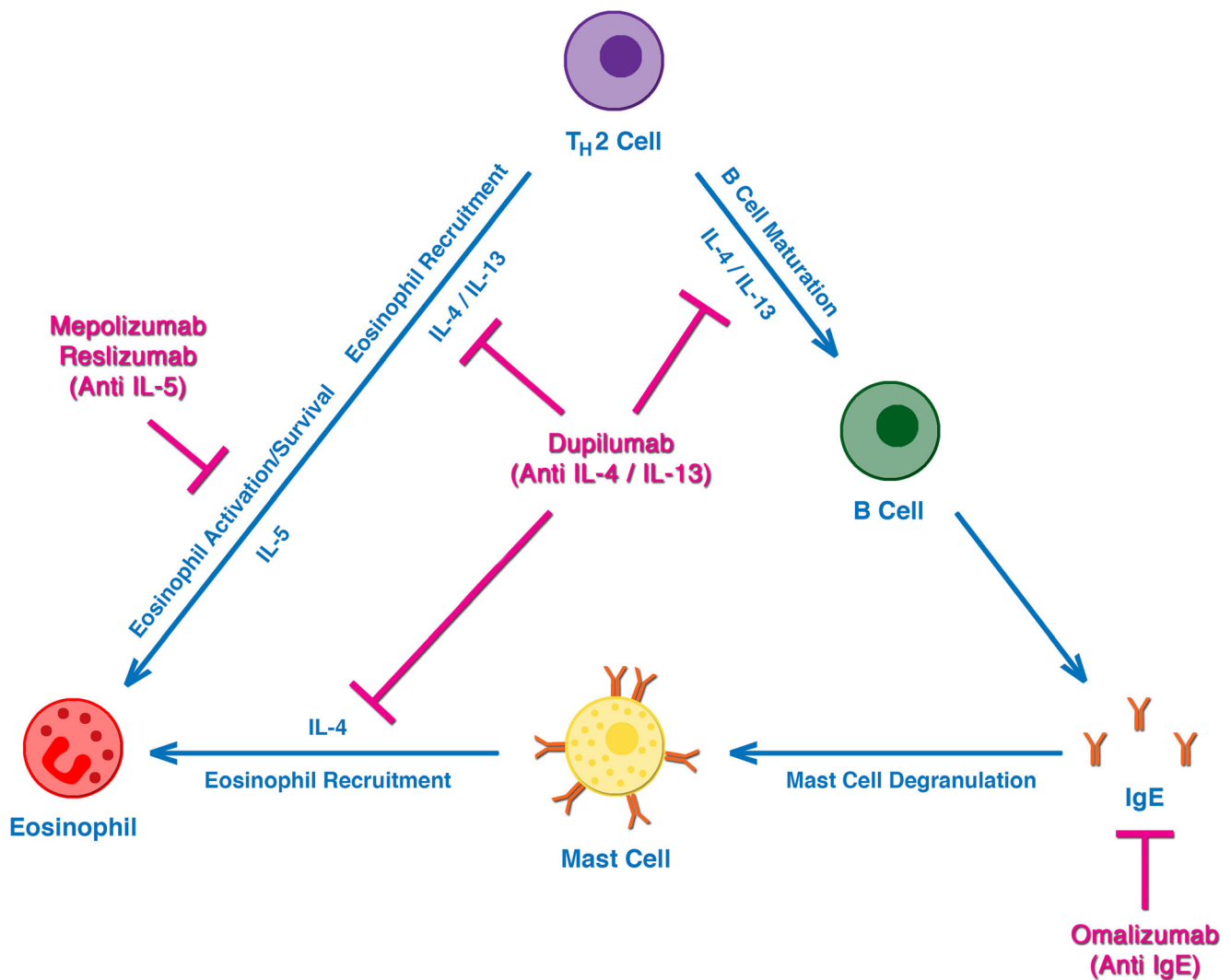


Fig. 2 Summary of nasal polyposis pathophysiology and monoclonal antibody targets

CRSwNP is defined by the presence of two of the above symptoms for over 12 weeks and polyps visualized bilaterally on endoscopy [17]. Due to the predominance of these symptoms, it is important that patients have improvement in these measures when measuring the efficacy of therapeutic options. This is often measured subjectively on symptom score scales, such as the SinoNasal Outcome Test, Visual Analog Scale, RhinoQOL, and the University of Pennsylvania Smell Identification Test. These scales often use Likert scales, which is a scale of 0 to 5, with 0 for no problem with the symptom and 5 for the symptom creating a problem that is bad as it can be.

Nasal polyp score (NPS) is measured by endoscopic evaluation of the extent of polyps within the nasal cavity. The original score that was measured in the phase III clinical trials of mometasone nasal spray graded each nasal fossa as 0 for no polyps, 1 for polyps in the middle meatus not reaching below the inferior border of the middle turbinate, 2 for polyp reaching below the inferior border of the middle turbinate but not the inferior border of the inferior turbinate, or 3 for

large polyp reaching to or below the lower border of the inferior turbinate. The scores from each side were summed for a possible score range of 0 to 6. This scoring system is somewhat subjective in that it depends on operator technique and timing in the nasal cycle, which may affect relative location and, therefore, grading of polyps [13].

The Lund-Mackay score serves to assist clinicians in determining severity of mucosal swelling and the appropriate therapeutic approach. It grades the five sinuses on CT to determine a total score. Sinuses are assigned a score of 0 for totally patent, 1 for partial opacification, or 2 for complete opacification. The osteomeatal complex (OMC) is graded as 0 for not occluded or 2 for occluded. Total score ranges from 0 to 24 and represents the summed score of the sinuses and OMCs bilaterally. Lund-Mackay was found to have higher interscorer agreement and ease of use when compared with other disease grading systems, such as Jorgensen or May-Levine. The original Lund-Mackay score is not sensitive to change within the partial opacification category (i.e., both 1%

partial opacification and 99% partial occlusion would be assigned a score of 1 for the sinus in question); therefore, a modified Lund-Mackay score was developed, which subcategorizes partial opacification. Three-dimensional volumetric scoring systems do exist and are believed to be the most accurate objective measures of disease. However, these systems require significant operator training and are limited by access to software [18].

Therapeutic Antibodies

With the success of monoclonal antibodies in other chronic eosinophilic diseases, researchers have investigated the efficacy of these drugs in the treatment of nasal polyposis (Table 1). The monoclonal antibodies omalizumab (anti IgE), dupilumab (anti IL-4R α), and reslizumab and mepolizumab (both anti IL-5) specifically target key players in the pathophysiology of NP. Although none of these drugs are currently approved for the treatment of nasal polyposis, they are in clinical development for this indication.

Omalizumab

Omalizumab is a humanized monoclonal antibody that binds free-circulating IgE, inhibiting the binding of IgE to the high-affinity IgE receptor. Omalizumab also downregulates the expression of IgE receptors on the surface of mast cells, basophils, and dendritic cells [22]. IgE cross-linking results in mast cell degranulation; therefore, inhibiting IgE reduces downstream inflammatory mediators released by mast cells, such as IL-4. Omalizumab was originally approved in 2003 for patients with treatment-resistant, moderate to severe allergic asthma [23, 24]. Since then, it has been approved for patients with chronic idiopathic urticaria that is not controlled by antihistamine (anti-H1) treatment [25]. Initial reports of the benefit of omalizumab on nasal polyposis came from several small case series in which subjects receiving omalizumab for their asthma were observed to have decreased size of their comorbid nasal polyps and less requirement for intranasal corticosteroid sprays [26, 27]. Subsequently, a randomized, double-blind, placebo-controlled trial ($n = 24$) [19] was conducted to investigate the efficacy of omalizumab in patients with nasal polyps and comorbid asthma over a 16-week period. A significant decrease in total nasal endoscopic polyp score was seen in the omalizumab-treated group compared with the placebo group from week 8 and onward (week 8, $P = .03$; week 12, $P = .04$; and week 16, $P = .005$). This objective measurement was confirmed by CT evaluation using the Lund-Mackay score ($P = .005$). In the omalizumab-treated group, symptom scores decreased for nasal congestion ($P = .002$), anterior rhinorrhea ($P = .003$), and loss of sense of smell ($P = .004$). Other outcomes measured in this study were serum

and local mucosal inflammatory markers, but these were not improved significantly by the treatment. Interestingly, the study analyzed the effect of omalizumab in patients stratified into “allergic” and “non-allergic” categories based on skin prick test. After 16 weeks, both groups showed a significant decrease in total polyp score and clinical symptoms. The most commonly observed adverse event in the study was an upper respiratory infection (URI), and no serious adverse events were reported. A shortcoming of this study was including only patients with severe nasal polyposis and comorbid asthma, so the results cannot be generalized to NP patients without concurrent asthma.

Omalizumab is currently in phase III trials for the indication of CRSwNP. These two double-blind, placebo-controlled trials, “POLYP 1” and “POLYP 2,” are evaluating a total of 265 adult subjects with treatment-resistant nasal polyposis, measuring two co-primary endpoints of nasal congestion symptoms and an intranasal polyp score over 24 weeks of treatment [28, 29]. An open-label extension trial of POLYP 1 and POLYP 2 is currently in recruitment [30].

Dupilumab

Dupilumab is a fully human monoclonal antibody targeting the IL-4 receptor α -subunit. This receptor subunit is shared by the IL-4 and IL-13 receptors. Therefore, signaling of both interleukins is inhibited by dupilumab, with the goal of reducing the Th2-mediated inflammation. In March of 2017, dupilumab was approved for treatment of patients with moderate to severe atopic dermatitis whose symptoms are not controlled with topical prescription therapies [31]. A randomized, double-blind, placebo-controlled parallel group study [20] was executed with 60 patients who had nasal polyposis refractory to corticosteroids. The experimental group was given a loading dose of dupilumab followed by weekly injections. Both experimental and control groups received concomitant mometasone furoate nasal spray. The study period was 16 weeks. The change in bilateral endoscopic nasal polyp score was statistically significant between the two treatment groups (LS mean difference between groups, -1.6 [95% CI, -2.4 to -0.7]; $P < .001$). Clinical symptoms evaluated by the SinoNasal Outcome Test (LS mean difference between groups, -18.1 [95% CI, -25.6 to -10.6]; $P < .001$) and sense of smell measured by the University of Pennsylvania Smell Identification Test (LS mean difference between groups, 14.8 [95% CI, 10.9 to 18.7]; $P < .001$), both showed significant improvements. The study also looked at serum biomarkers and saw a statistically significant decrease in the levels of total serum IgE in the treatment group when compared with the placebo group ($P < .001$). Adverse events were reported in 25/30 patients in the placebo group and 30/30 in the treatment group, which most commonly included nasopharyngitis, injection site reactions, and headache.

Table 1 Biologics for nasal polyposis

Drug name	Target	Mechanism of action	Randomized double-blind, placebo-controlled clinical trial results			Current status of drug development
			Authors	Dosing	Subjects	Outcome
Omalizumab	IgE	Humanized monoclonal (IgG1) antibody that binds free-circulating IgE and inhibits the binding of IgE to the high-affinity FcεRI on the Cε3 domain, also decreases IgE receptors on mast cells, basophils, and dendritic cells.	Gevaert, P., et al. 2013. [19]	Weight- and serum IgE-based dosing every 2–4 weeks for 16 weeks, observation for total of 20 weeks	24 adults with CRSwNP and asthma; serum IgE 30 to 700 µg/mL	Improved nasal polyp score at 16 weeks (primary endpoint). Improved Lund-Mackay CT score, decreased nasal congestion, decreased loss of smell, and decreased anterior rhinorrhea Improved SF-36, RSOM-31, and AQLQ scores
Dupilumab	IL-4Rα	Fully human monoclonal antibody to the IL-4 receptor α-subunit which is common to the receptors of both IL-4 and IL-13	Bachert, C., et al. 2016. [20]	600 mg subcutaneous loading dose; 300 mg weekly for 15 additional weeks	60 adults with bilateral, uncontrolled CRSwNP	Improved nasal polyp score at week 16 (primary endpoint); improved Lund-Mackay CT score and SNOT-22 score; improved sense of smell, decreased nasal congestion, and decreased posterior rhinorrhea; decreased maxillary volume occupied by disease; increased morning peak nasal inspiratory flow rate
Reslizumab	IL-5	Humanized monoclonal IL-5 (IgG4κ) antibody that binds IL-5 and prevents it from binding to the IL-5 receptor α-subunit on the surface of eosinophils	Gevaert, P., et al. 2006. [9]	3 mg/kg intravenous or 1 mg/kg intravenous administered as single dose, observation for 36 weeks following dose	24 adults with bilateral nasal polyposis or recurrent nasal polyps after sinus surgery	Phase I trial: not designed for evaluation of efficacy; no difference in the symptom scores or in the nasal peak inspiratory flow values at any time point in either treatment group when compared with placebo; rebound eosinophilia occurred after 24 or 32 weeks Phase II trial: not designed for evaluation of efficacy; no difference in the symptom scores or in the nasal peak inspiratory flow values at any time point in either treatment group when compared with placebo; rebound eosinophilia occurred after 24 or 32 weeks A phase III trial is recruiting for the indication of chronic rhinosinusitis.
Mepolizumab	IL-5	Humanized monoclonal IL-5 (IgG1κ) antibody that binds IL-5 and prevents it from binding to the IL-5 receptor α-subunit on the surface of eosinophils	Bachert, C., et al. 2017. [21]	750 mg intravenous every 4 weeks for 6 doses; observation for total of 25 weeks	105 adults with severe, bilateral nasal polyposis requiring surgery	More patients in the mepolizumab group no longer met the criteria for requiring surgery (30% versus 10% in placebo group) at week 25 (primary endpoint). Improved nasal polyp score and symptom scores for rhinorrhea, nasal obstruction, and sense of smell; no rebound eosinophilia at week 25 (4 weeks after last dose) Phase III trial currently recruiting participants for use with background mometasone furoate nasal spray for the indication of severe bilateral nasal polyposis
Benralizumab	IL-5Rα	Humanized monoclonal IL-5Rα (IgG1κ) antibody that binds IL-5 receptor α-subunit on eosinophils, preventing binding of IL-5	No published studies in nasal polyposis			Phase III trial currently recruiting participants for use with concomitant mometasone furoate for indication of chronic rhinosinusitis with nasal polyposis

Dupilumab has just completed two phase III trials for use with background mometasone furoate nasal spray for the indication of nasal polyps. The studies had two primary endpoints: change from baseline in nasal congestion/obstruction (NC) symptom severity score by daily patient assessment and change from baseline in nasal polyposis score (NPS) as assessed by nasal endoscopy. Both of these primary endpoints were met, per initial data released from the manufacturer [32, 33].

Biologics Targeting IL-5 (Reslizumab, Mepolizumab, Benralizumab)

Reslizumab is a humanized anti-IL-5 antibody that binds circulating IL-5 and prevents its binding to the α -subunit of the IL-5 receptor. This prevents the differentiation, survival, and life prolongation of eosinophils. In March 2016, reslizumab was given FDA approval for add-on maintenance treatment in patients with severe asthma aged 18 years and older with an eosinophilic phenotype [34, 35]. A study published in 2006 sought to determine the effect of reslizumab in patients with “massive nasal polyps.” In this randomized, double-blind, placebo-controlled study ($n=24$) [9], the experimental group was administered a single intravenous infusion (1 mg/kg or 3 mg/kg) of reslizumab and followed for 36 weeks. The primary outcome of this trial was an improvement in nasal polyp score. Reslizumab decreased blood eosinophil count in both dosage groups as early as 8 h post-infusion when compared with placebo, and this was sustained for up to 8 weeks ($P<.01$). Notably, after 24 weeks (1 mg/kg) or 32 weeks (3 mg/kg), increased eosinophil counts to levels higher than baseline occurred ($P<.05$). While, at the end of the study, there was no significant reduction in total polyp score in any group, the 1 mg/kg group did show a temporary decrease in total polyp score during the trial. During post-study analysis, it was found that “responders”—those who had the best improvement on reslizumab—had baseline nasal secretion IL-5 levels greater than 40 pg/mL (odds ratio, 21.0 [95% CI 1.5 to 293.3]; $P=.009$). Fifty-eight percent of participants experienced an adverse event, most commonly URI, without any significant difference between the placebo or two treatment groups.

Reslizumab may improve nasal polyp score and symptoms in patients with higher IL-5 levels in their nasal secretions. However, assessing nasal IL-5 levels is not very feasible in clinical practice and might limit its application compared with other monoclonal antibody therapies. While there are no current trials for reslizumab in the treatment of nasal polyposis, a phase III trial for reslizumab in chronic rhinosinusitis is currently in recruitment phase [36].

Mepolizumab is a humanized anti IL-5 antibody with a mechanism of action similar to that of reslizumab, though it has been developed as a subcutaneous injection rather than an intravenous infusion. In November 2015, the drug was given FDA approval for add-on maintenance treatment of patients

with severe asthma aged 12 years and older and with an eosinophilic phenotype [21]. A study published in 2011 [37] evaluated mepolizumab as a treatment for severe nasal polyposis in 30 patients with CRSwNP. In this randomized, double-blind, placebo-controlled study, the experimental group was given two injections of the drug 28 days apart after an initial run-in period of 4–12 weeks. The primary outcome of this study was reduction in NP score at 4 weeks after the second injection. Secondary outcomes included change in CT score, nasal peak inspiratory flow, and total symptom score. In addition, the peripheral blood eosinophil counts and serum and nasal secretion cytokine levels were measured. Total polyp score was significantly decreased in the treatment group ($P=.028$). No other outcomes reached statistical significance. However, no rebound eosinophilia as noted in the previous trial of reslizumab was observed. Of note, there was a significant dropout rate during the course of the study, which may have contributed to the lack of a significant difference between groups. During the study, 16/30 patients experienced at least one adverse event, most commonly URI, which was experienced by 5/20 patients in the experimental group and 1/10 patients in the placebo group without reaching statistical significance between groups.

Another trial [38] of mepolizumab was published in 2017 to evaluate the reduction in need for surgery in patients with severe nasal polyposis. All participants were eligible for revision polypectomy due to recurrent nasal polyposis refractory to intranasal corticosteroids. Both experimental and control groups used nasal steroids during the 14-day run-in period and for the length of the study. Patients were followed for 25 weeks and were administered mepolizumab injection or placebo at week 1 and every 4 weeks thereafter, with the final dose on week 21. The primary endpoint was the decrease in the number of patients who no longer met criteria for surgery based on NP score and NP severity assessed by a Visual Analog Score (VAS) at 25 weeks. Secondary endpoints included other symptomatic improvements of NP. The mepolizumab group showed a significant reduction in need for surgery at 25 weeks as compared with the control group ($P=.006$). There was also significant improvement of individual symptom scores in the mepolizumab group as early as week 5 (nasal blockage and rhinorrhea, $P\leq.05$) or week 9 (postnasal drip, $P\leq.001$; loss of smell, $P\leq.05$). This improvement was still significant at the end of the trial (nasal blockage, $P\leq.01$; all others, $P\leq.001$). Some participants became “responders” (by symptomatic improvement and reduced need for surgery) for the first time at 25 weeks. The investigators noted that, perhaps, further long-term studies should be conducted since there was no long-term follow-up and certain participants converted to responder status late in the trial.

A phase III trial for mepolizumab in nasal polyposis is currently recruiting participants. This long-term study intends to enroll 400 participants and will include subcutaneous

injection of mepolizumab every 4 weeks with background mometasone furoate nasal spray for 52 weeks. Its primary outcomes include change from baseline total endoscopic nasal polyp score and change in VAS score of nasal obstruction. Secondary outcomes include time to first nasal surgery after drug cessation. Given the existing and planned studies, mepolizumab could serve to improve nasal symptoms in nasal polyposis, reduce need for nasal polypectomy, or delay the need for nasal polypectomy in NP patients.

Benralizumab is another monoclonal antibody targeting IL-5 activity. Specifically, it is a humanized monoclonal antibody against the α -subunit of the IL-5 receptor. It is approved for use in adolescents and adults with severe eosinophilic-type asthma. A recent post hoc analysis of the two trials of benralizumab in severe eosinophilic asthma examined those subjects with nasal polyposis versus those without NP. It found that benralizumab resulted in greater improvement in asthma exacerbation rate and lung function in subjects with nasal polyps than in those without polyps [39]. However, nasal polyp outcome measures were not examined. A phase III double-blind, placebo-controlled trial of benralizumab with background mometasone furoate for treatment of severe nasal polyposis is currently recruiting subjects [40].

Biologics Targeting IL-33

As the second wave of biologics targeting Th2-mediated inflammation make their way down the investigational pipeline, they are likely to be trialed for their efficacy in treating CRSwNP. One of these already being considered for use in CRSwNP is AMG 282, which is an anti-ST2 monoclonal antibody, inhibiting the binding of IL-33 to the ST2 receptor. IL-33 is expressed by basal epithelial and endothelial cells, functioning as an “alarmin” to alert the immune system, particularly innate immune cells (innate lymphocyte cells type-2 (ILC-2)) and Th2 cells, to damage or stress [41]. A phase I study assessing the safety and tolerability of AMG 282 in healthy volunteers and in subjects with CRSwNP has been recently completed [42]. While no current phase II trial of AMG 282 in nasal polyposis appears to be underway, another monoclonal antibody targeting IL-33, etokimab, will be evaluated for use in adults with chronic rhinosinusitis with nasal polyposis in an upcoming phase II double-blind, placebo-controlled trial [43].

Discussion

As shown above, therapeutic antibodies have shown promise toward improving the management and treatment of nasal polyposis. However, at this time, none of the drugs are FDA-approved for NP. Investigation of the drugs has elucidated that

the contributions of IL-4, IL-5, IL-13, and IgE as disease mediators might be significant in the pathogenesis of NP.

One of the unknowns in nasal polyposis is the exact contribution of genetics and expression of certain mediators in each individual patient's disease, resulting in different phenotypes and endotypes. For example, some patients have a genetic tendency to produce high levels of IL-4, making that mediator a more important target for their treatment. On the other hand, other patients might tend to make high levels of IL-5 and have otherwise normal expression of IL-4. These patient groups may have comparable symptoms and objective polyp scores, but the approach to their therapy might be different using highly specific therapeutic antibodies. An important point is that this does not mean that these patient groups suffer from different diseases, but rather that the disease process is heterogeneous, in terms of the weight of different cytokines contributing to a similar inflammatory process, and different individuals may require therapy targeting different mediators.

Because expression of these mediators varies among patients, determining a clinically realistic biomarker that would predict drug efficacy is important. In the currently completed trials, there was no biomarker identified in nasal secretions or serum that predicted response to treatment, with the exception of IL-5 levels in the nasal secretions. A conceivable barrier toward using a single nasal biomarker is the potential for this biomarker to have a lesser apparent concentration due to dilution by increased nasal secretions in patients with nasal polyposis, but increased absolute expression, or an increased concentration in the tissue but not in the secretions. Furthermore, while the reslizumab trial showed the best response among patients with increased baseline IL-5 in nasal secretions, a test to obtain this value may be neither readily available nor practical for broad implementation in a clinical setting. Therefore, in order for these drugs to be marketable as a future treatment option, a more feasible biomarker might need to be identified for each monoclonal antibody.

Future clinical trials should consider larger sample sizes, longer duration of treatment, longitudinal follow-up after treatment, and direct comparison between the monoclonal antibodies, or comparing them with intranasal corticosteroids, which are the current standard of medical treatment. Some of the previous clinical trials, either conducted or underway, use concomitant mometasone furoate for both experimental and control groups. Mometasone furoate does not require potential phenotyping or endotyping by biomarker expression—corticosteroids work by more broadly downregulating multiple Th2 inflammatory mediators that contribute to NP and are not as specific as the therapeutic antibodies. Dosage, frequency, and duration of monoclonal antibody treatment might also need to be adjusted for improved efficacy and safety.

Additionally, while the current trials have demonstrated initial efficacy and safety, novel treatment approaches inherently contain high risk for unknown long-term side effects to surface when patients are treated for a longer duration or in

greater numbers. However, these uncertainties are typical for novel treatments in clinical development and should not distract from the enormous clinical value that new treatment options bring to NP patients. For many, the only FDA-approved treatment option, intranasal mometasone furoate and fluticasone propionate corticoid steroids, is not sufficient in providing enough symptomatic relief for NP and associated diseases, such as bronchial asthma and allergic rhinitis. After medical management is deemed inadequate, physicians often turn to off-label systemic steroids or surgery, with potential morbidity and high recurrence rates.

Conclusion

Nasal polyposis poses a great burden on the quality of life of patients. The current FDA-approved medical treatment for NP using intranasal corticosteroids is inadequate in many patients. Monoclonal antibody therapies targeting several crucial mediators of NP pathogenesis have shown success in phase II and III clinical trials, and now bring hope for an exciting new treatment option urgently needed.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflicts of interest.

References

1. Fokkens W, Lund V, Mullol J, European Position Paper on Rhinosinusitis and Nasal Polyps group (2007) European position paper on rhinosinusitis and nasal polyps 2007. *Rhinol Suppl* 20:1–136
2. Johnson JT, Rosen CA, Bailey BJ (2014) Bailey's head and neck surgery—otolaryngology. Wolters Kluwer Health/Lippincott Williams & Wilkins, Philadelphia, p 1 online resource (2 volumes)
3. Zhang Y, Gevaert E, Lou H, Wang X, Zhang L, Bachert C, Zhang N (2017) Chronic rhinosinusitis in Asia. *J Allergy Clin Immunol* 140:1230–1239
4. Bachert C, Gevaert P, Hellings P (2017) Biotherapeutics in chronic rhinosinusitis with and without nasal polyps. *J Allergy Clin Immunol Pract*
5. Claus B, Wagenmann M, Ulrich H, Claudia R (1997) IL-5 synthesis is upregulated in human nasal polyp tissue. *J Allergy Clin Immunol* 6(99):837–842
6. Oboki K, Nakae S, Matsumoto K, Saito H (2011) IL-33 and airway inflammation. *Allergy Asthma Immunol Res* 3(2):81–88
7. Rankin S, Conroy DM, Williams TJ (2000) Eotaxin and eosinophil recruitment: implications for human disease. *Mol Med Today* 6:20–27
8. Lezcano-Meza D, Dávila-Dávila B, Vega-Miranda A, Negrete-García MC, Teran LM (2003) Interleukin (IL)-4 and to a lesser extent either IL-13 or interferon-gamma regulate the production of eotaxin-2/CCL24 in nasal polyps. *Allergy* 58:1011–1017
9. Gevaert P et al (2006) Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol* 118(5):1133–1141
10. (2016) Adult chronic rhinosinusitis: definitions, diagnosis, epidemiology, and pathophysiology. *Otolaryngol Head Neck Surg*. 129(3 suppl):S1–S32
11. Ponikau JU, Winter L, Kephart GM, Squillace DL, Hershcovitch MD, Moon S, Sherris DA, Kern EB, Gleich GJ, Kita H (2015) An immunologic test for chronic rhinosinusitis based on free intranasaleosinophilic major basic protein. *Int Forum Allergy Rhinol* 5:28–25
12. Small CB et al (2005) Efficacy and safety of mometasone furoate nasal spray in nasal polyposis. *J Allergy Clin Immunol* 116(6):1275–1281
13. Stjärne P, Mösges R, Jorissen M, Passali D, Bellussi L, Staudinger H, Danzig M (2006) A randomized controlled trial of mometasone furoate nasal spray for the treatment of nasal polyposis. *Arch Otolaryngol Head Neck Surg* 132:179–185
14. Chatham W (2017) Glucocorticoid effects on the immune system. In: Orange J, Marr KA (eds) UpToDate
15. Saag K, Furst ME (2017) Major side effects of systemic glucocorticoids. In: Matteson E (ed) UpToDate,
16. DeConde AS, Mace JC, Levy JM, Rudmik L, Alt JA, Smith TL (2017) Prevalence of polyp recurrence after endoscopic sinus surgery for chronic rhinosinusitis with nasal polyposis. *Laryngoscope* 127(3):550–555
17. Fokkens WJ et al (2012) European position paper on rhinosinusitis and nasal polyps 2012. A summary for otorhinolaryngologists. *Rhinology* 50(1):1–12
18. Likness MM, Pallanch JF, Sherris DA, Kita H, Mashtare TL Jr, Ponikau JU (2014) Computed tomography scans as an objective measure of disease severity in chronic rhinosinusitis. *Otolaryngol Head Neck Surg* 150(2):305–311
19. Gevaert P, Calus L, van Zele T, Blomme K, de Ruyck N, Bauters W, Hellings P, Brusselle G, de Bacquer D, van Cauwenberge P, Bachert C (2013) Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 131(1):110–6 e1
20. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, Hellings P, Jiao L, Wang L, Evans RR, Pirozzi G, Graham NM, Swanson B, Hamilton JD, Radin A, Gandhi NA, Stahl N, Yancopoulos GD, Sutherland ER (2016) Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 315(5):469–479
21. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald J, Chetta A, Humbert M, Katz LE, Keene ON, Yancey SW, Chanez P, MENSA Investigators (2014) Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 371(13):1198–1207
22. Beck LA, Marcotte GV, MacGlashan Jr D, Togias A, Saini S (2004) Omalizumab-induced reductions in mast cell FcεR1 expression and function. *J Allergy Clin Immunol* 114(3):527–530
23. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, van As A, Gupta N (2001) Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 108(2):184–190
24. Humbert M, Beasley R, Ayres J, Slavov R, Hébert J, Bousquet J, Beeh K-M, Ramos S, Canonica GW, Hedegcock S, Fox H, Bogg M, Surrey K (2005) Benefits of omalizumab as add-on therapy in

- patients with severe persistent asthma who are inadequately controlled despite best available therapy (GINA 2002 step 4 treatment): INNOVATE. *Allergy* 60:309–316
25. Saini SS, Bindslev-Jensen C, Maurer M, Grob JJ, Bülbül Baskan E, Bradley MS, Canvin J, Rahmaoui A, Georgiou P, Alpan O, Spector S, Rosén K (2015) Efficacy and safety of omalizumab in patients with chronic idiopathic/spontaneous urticaria who remain symptomatic on H1 antihistamines: a randomized, placebo-controlled study. *J Invest Dermatol* 135(1):67–75
 26. Penn R, Mikula S (2007) The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. *Am J Rhinol* 21:428–432
 27. Vennera M, Picado C, Mull J et al (2011) Efficacy of omalizumab in the treatment of nasal polyps. *Thorax* 66:824–825
 28. Identifier NCT03280550. A clinical trial of omalizumab in participants with chronic rhinosinusitis with nasal polyps (POLYP 1). National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 29. Identifier NCT03280537. A clinical trial of omalizumab in participants with chronic rhinosinusitis with nasal polyps (POLYP 2). National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 30. Identifier NCT03478930. An extension study of omalizumab in participants with chronic rhinosinusitis with nasal polyps. National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 31. Simpson EL, Bieber T, Guttman-Yassky E, Beck LA, Blauvelt A, Cork MJ, Silverberg JJ, Deleuran M, Kataoka Y, Lacour JP, Kingo K, Worm M, Poulin Y, Wollenberg A, Soo Y, Graham NM, Pirozzi G, Akinlade B, Staudinger H, Mastey V, Eckert L, Gadkari A, Stahl N, Yancopoulos GD, Ardeleanu M, SOLO 1 and SOLO 2 Investigators (2016) Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med* 375(24):2335–2348
 32. Identifier NCT02898454. Controlled clinical study of dupilumab in patients with nasal polyps (SINUS-52). National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 33. Identifier NCT02912468. Controlled clinical study of dupilumab in patients with nasal polyps (SINUS-24). National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 34. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M (2016) Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest* 150(4): 799–810
 35. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, Murphy K, Maspero JF, O'Brien C, Korn S (2015) Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med*
 36. Identifier NCT02799446. Effect of Reslizumab in Chronic Rhinosinusitis. National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 37. Gevaert P et al (2011) Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 128(5):989–95 e1–8
 38. Bachert C, Sousa AR, Lund VJ, Scadding GK, Gevaert P, Nasser S, Durham SR, Cornet ME, Kariyawasam HH, Gilbert J, Austin D, Maxwell AC, Marshall RP, Fokkens WJ (2017) Reduced need for surgery in severe nasal polyposis with mepolizumab: randomized trial. *J Allergy Clin Immunol* 140:1024–1031.e14
 39. Maspero JEA Clinical efficacy of benralizumab in patients with severe, uncontrolled eosinophilic asthma and nasal polyposis: pooled analysis of the SIROCCO and CALIMA trials. *J Allergy Clin Immunol* 141(2):AB12
 40. Identifier NCT03401229. Efficacy and safety study of benralizumab for patients with severe nasal polyposis. National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 41. Miller AM (2011) Role of IL-33 in inflammation and disease. *J Inflamm (Lond)* 8(1):22
 42. Identifier NCT02170337. A study to evaluate the safety, tolerability, pharmacokinetics, and pharmacodynamics of AMG 282 in healthy subjects and subjects with chronic rhinosinusitis with nasal polyps. National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019
 43. Identifier NCT03614923. Etokimab in adult patients with chronic rhinosinusitis with nasal polyps (CRSwNP). National Library of Medicine: [ClinicalTrials.gov](https://clinicaltrials.gov). Accessed 24 April 2019

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