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Biologics for the Treatment of Allergic Rhinitis, Chronic Rhinosinusitis, and Nasal Polyposis

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Keywords

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Introduction

Allergic rhinitis (AR), many presentations of chronic rhinosinusitis (CRS), and most presentations of CRS with nasal polyposis (NP) are recognized as type 2 (T2) inflammatory diseases. These T2^{high} inflammatory conditions are characterized by infiltration with eosinophils, basophils, mast cells, and other inflammatory cells and are recognized by the robust expression of cytokines associated with Th2 effector cells, specifically the interleukins (IL) IL-4, IL-5, and IL-13. The term T2^{high} is now the preferred term for this inflammatory phenotype, in recognition of the numerous additional sources of Th2 effector cytokines such as innate lymphoid 2 cells (ILC2s), eosinophils, mast cells, and numerous others. Although not specifically developed for T2 diseases of the upper airway, recognition of the roles of these T2 cytokines in driving the presence and severity of these conditions has led to the exploration of biologics that were developed for other T2 conditions (atopic dermatitis (AD) and asthma) as therapeutic options. This chapter will review the use of biologics as potential interventions in allergic rhinitis, chronic rhinosinusitis, and nasal polyposis.

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Biologics in the treatment of allergic rhinitis

Allergic rhinitis is in large part an allergic disorder mediated by specific IgE directed against aeroallergens. However, AR is also a quintessential T2 disorder with this type 2 cytokine expression being driven not only by allergen-specific Th2 effector lymphocytes but also by nasal stromal cells and recruited immune cells. And it is this T2^{high} state driving the recruitment of basophils, mast cells, eosinophils, ILC2 cells, and numerous other inflammatory cells that along with the allergic/IgE-mediated component, is responsible for the full expression of the upper airway, ocular, and lower airway symptoms. To the extent that AR is driven by aeroallergen-specific IgE, it is the cross-linking of surface IgE and the consequent mast and basophil degranulation that leads to the release of the vasoactive and other proinflammatory mediators that strongly contribute to the symptoms of AR.

Omalizumab (humanized anti-IgE antibody) binds to IgE and thereby captures IgE antibodies and prevents their binding to the high-affinity receptor (FcεRI). Reduced binding of IgE leads to the disassociation of the high-affinity receptor and thereby dramatically decreases the expression of FcεRI on mast cells and basophils, as well as on antigen-presenting cells. This decreased availability of surface IgE on antigen-presenting dendritic cells and B cells interferes with IgE antibody-mediated facilitated antigen capture and thereby contributes to the amelioration of Th2 activation and the T2^{high} state.¹ All of these effects make omalizumab an inviting treatment for allergic rhinitis refractory to the conventional therapies of oral antihistamines, intranasal steroids, and intranasal antihistamines/cromolyn.

Although only FDA approved for the treatment of moderate-to-severe persistent asthma and chronic idiopathic urticaria, omalizumab has been extensively studied in the treatment of AR both as a direct and as an add-on therapy. In a recent review and meta-analysis by Yu *et al.*², 83 articles were identified regarding omalizumab for the treatment of AR and, of these, 16 were randomized controlled trials. These latter 16 studies were used the focus of their analysis and these involved a total of 3458 patients (1931 experimental and 1527 control subjects). Their analysis showed statistically significant differences between the omalizumab and control groups in daily nasal symptom score, daily ocular symptom score, daily nasal medication symptom scores, proportion of days of emergency drug use, rhinoconjunctivitis-specific quality of life questionnaires, and overall evaluation (Table 1). Importantly, there was no statically significant difference in adverse events.²

Additionally, omalizumab has been studied in patients receiving allergen immunotherapy (AIT). This is based upon the argument that neutralization of IgE and reduced IgE receptor expression on mast cells and basophils should either eliminate or greatly reduce the severity of AIT-associated allergic reactions, including anaphylaxis. Omalizumab significantly improved the redness and swelling at immunotherapy injection sites and improved daily allergy severity scores.² Efficacy in preventing anaphylaxis was specifically studied using a rush AIT protocol. Rush immunotherapy is a process in which patients serially receive AIT injections, typically in a single day, to rapidly achieve maintenance concentrations. While often useful, rush IT is associated with a high risk for local and systemic allergic reactions. Casale *et al.* found that omalizumab pretreatment reduced the adverse events associated with AIT and significantly reduced anaphylaxis (odds ratio 0.17, p=0.026).³ This result argues

that similar results could be achieved with conventional AIT when used for treatment of AR (and asthma).

None of the other T2-targeting biologics have been specifically studied in AR. A handful of studies have assessed the efficacy of other T2-targeting biologics for the treatment of AR in the setting of comorbid asthma. Dupilumab (discussed in more detail below) is an anti-IL-4 receptor α (IL-4R α) antibody that when dosed at 300 mg every 2 weeks was shown by Weinstein *et al.* to significantly reduce AR-associated symptoms in patients with comorbid asthma.⁴ Only a non-statistically significant trend was observed at the 200 mg dosing. Of note, no differences in asthma control were seen in subjects treated with either dose of dupilumab if they lacked comorbid perennial allergic rhinitis.⁴

No compelling studies of the IL-5/IL-5R-targeting biologics have been performed in AR. While AR is often viewed in an over-simplified fashion as a purely IgE/mast cell-mediated disease, AR is strongly associated with the influx of eosinophils and attenuation of this eosinophilia underlies much of the efficacy of corticosteroids. As such, there is an argument for expecting efficacy from IL-5/IL-5R-targeting therapies in AR. In one study, although no specific analysis of nasal symptoms was reported, mepolizumab (humanized anti-IL-5 antibody) significantly reduced not only asthma exacerbations but also improved quality of life assessments in patients with severe asthma and self-reported upper airway disease.⁵

Chronic rhinosinusitis without nasal polyps

Although extensively studied in CRSwNPs the efficacy of biologics in CRS without NPs is unexplored and remains theoretical. The failure to study biologics in CRSsNPs is largely based on the somewhat specious dogma that views CRSwNPs exclusively as a type 2 inflammatory (interleukin (IL)-4^{high}/IL-5^{high}/IL-13^{high}) disease in contrast to CRSsNPs which is typically viewed as a type 1 (interferon (IFN)- γ ^{high} and/or type 3 (IL-17^{high}) disease.⁶ As a consequence, CRSsNPs has typically not been considered an appropriate focus for type 2-targeting biologics. Current studies provide compelling evidence against this oversimplified view of these conditions. For example, in a European study of CRSwNPs only 62% of NPs demonstrated only the type 2 cytokine IL-5, an additional 23% were combinations of type 2 with type 1 (IFN- γ) and/or type 3 (IL-17) cytokines and fully 15% had no IL-5.⁷ Similarly, in a North American study the identical 62% of CRSwNPs patients were shown to have isolated type 2 disease.⁸ The converse is true for CRS in the absence of NPs. Thus, in this European study⁷ 20% of subjects had isolated type 2 disease with additional 3% displaying mixed T2 patterns and in the North American study fully 34% had isolated T2 disease.⁸ Thus, arguably up to 38% of CRSwNP may be variably refractory to pure type 2 targeting biologics and a similar proportion of CRSsNP patients (20% - 34%) are currently being denied these agents which are likely to be quite effective.

The investigation of T2-targeting biologics in CRSsNPs will require identification and validation of biomarkers to predict those who are likely respond, as the basis for investigation. Although some of these responsive patients are likely to have concomitant asthma or elevations in blood absolute eosinophil counts, such parameters are likely to greatly under identify the potentially responsive population.⁹ One of the best predictors of

asthma responsiveness to biologics has been the identification of evidence for airway eosinophils, such as in induced sputum samples. Since functional endoscopic sinus surgery (FESS) is the mainstay of CRS therapy, a readily feasible approach to phenotyping CRSsNPs disease and predicting responsiveness to biologics is likely to have pathological tissue samples analyzed for eosinophil content. Given the cost of biologics it may similarly be reasonable to avoid their use in CRSsNP patients who have no evidence of eosinophilia on FESS-obtained tissue samples.

Biologics for Nasal Polyposis

Omalizumab

The concept that targeting IgE may be efficacious in the treatment of NPs is based on the high tissue expression of IgE in these disorders including both as active secretion by B and plasma cells and as surface IgE on mast cells.^{10,11} This tissue expression of IgE correlates with the severity of the disease and rapidity of post-surgical polyp recurrence. The target of this IgE is unclear as tissue IgE concentrations do not correlate with the presence of atopy and, indeed, a high proportion of these patients are not atopic.¹² One target of the IgE has been proposed to be directed against antigens derived from pathogens present in CRSwNP including *Staphylococcus aureus*^{13,14} and others.¹⁵ One of first randomized, controlled study of omalizumab for NPs in 2013 involved a 16-week trial with 16 patients on active treatment versus 8 on placebo.¹⁶ Omalizumab treatment was associated with a significantly lower total nasal endoscopic score. Importantly, presence of aeroallergen sensitization did not influence outcome. In 2016, Nsouli *et al.*¹⁷ conducted a 6-month trial involving 9 subjects with NPs and asthma. In this small study, the omalizumab cohort (n=5) demonstrated a 51% improvement in nasal endoscopic polyp scores (p<0.001) and a 25% improvement in nasal function (p<0.001). In a 2018 study, Bidder *et al.*¹⁸ evaluated upper airway efficacy of omalizumab in a cohort of severe asthmatics with co-existent CRSwNP. In this 16-week study, efficacy in improving the sinonasal outcome test (SNOT-22) was compared between 13 subjects who received omalizumab with 24 subjects treated with FESS and demonstrated similar improvements in both cohorts. Recently, two identical phase 3 clinical trials have been completed (Polyp 1/2) and their efficacy has recently been reported.¹⁹ In these randomized controlled trials involving a total of 265 subjects, omalizumab demonstrated compelling evidence for efficacy including significant improvement in both primary endpoints of change in average nasal congestion score as well as in endoscopically-ascertained nasal polyp scores at 24 weeks (Table 2).

Interleukin-5 and IL-5 receptor-targeting therapies: Mepolizumab / Reslizumab / Benralizumab

IL-5 is a key cytokine for the stimulation, maturation and survival of eosinophils. As previously discussed, elevated tissue eosinophilia and IL-5 levels are present in most patients with CRSwNP, making anti-IL5/IL-5R therapy an attractive potential treatment.

Mepolizumab

Mepolizumab is a humanized monoclonal antibody towards IL-5 which has shown promise in a number of studies related to CRSwNP. In a double-blind placebo controlled study,

patients with corticosteroid refractory NP (n=20) after treatment with mepolizumab demonstrated a reduction in total polyp score by 1.3 (± 1.72) vs 0.0 (± 0.94) in the placebo group (p=0.028).²⁰ This study also demonstrated a trend towards improvement in symptom scores for smell, congestion, and posterior pharyngeal drainage. An additional double-blind randomized study showed that treatment with mepolizumab reduced the need for surgery in patients with severe recurrent bilateral NP. After treatment (n=54), 30% of patients no longer met criteria for surgery based on endoscopic polyp scores and symptom severity scoring, compared to only 10% of the placebo group (n=51)(p=0.006).²¹ Additionally, in this same study patients treated with mepolizumab had significant reductions in SNOT-22 scores (-24.4 , n=32) when compared to placebo (-9.1 , n=42) (p=0.005). Another study investigating mepolizumab use in severe eosinophilic asthma demonstrated improvement in SNOT-22 scoring in patients both with (-13.7 , n=44) and without (-8.6 , n=160) NP at baseline after treatment with mepolizumab compared to placebo controls (-1.9 , (n=34) and -3.7 , (n=167), respectively).²²

Reslizumab

Reslizumab is also a humanized monoclonal antibody towards IL-5. In a small randomized controlled trial, 24 patients with bilateral NP received single doses of placebo or reslizumab at 1 or 3 mg/kg. Patients were noted to have improvement in total nasal polyp scores within 4–8 weeks, though the study was not sufficiently powered to determine significance.²³ At present, no other studies of this agent have been reported in regards to sinonasal outcome measures, although efficacy may be predicted based upon the high expression of IL-5 in NPs and efficacy of other IL-5-targeting agents.

Benralizumab

Benralizumab is a humanized monoclonal antibody towards the specific receptor subunit for IL-5, IL-5R α , and it is FDA approved for the treatment of severe eosinophilic asthma. It is being actively investigated for the treatment of CRSwNP but no efficacy studies have been reported. Two randomized double-blind placebo-controlled phase 3 clinical trials investigating benralizumab treatment for severe asthma underwent pooled subgroup analysis regarding nasal polyposis. These studies demonstrated that the presence of NP were independent predictors of enhanced efficacy of benralizumab treatment for severe asthma, separate from baseline peripheral blood eosinophilia.²⁴ Unfortunately, while NPs predicted greater efficacy for asthma, neither of these studies presented data for benralizumab for CRS or NP outcomes, although these observations invite further exploration.

Dupilumab

IL-4 and IL-13 are two key cytokines involved in the formation of nasal polyps in chronic rhinosinusitis. IL-4 promotes the terminal differentiation of naive T (Th0) cells into T helper 2 (Th2) cells, promotes their survival, and thereby strongly enhances the presence of a T2^{high} state. IL-4 also contributes to mast cell activation. In contrast, IL-13 contributes to eosinophil migration, goblet cell metaplasia, mucus gland hyperplasia, and mucus hypersecretion. As a result of these processes – and numerous others – together, these two cytokines drive processes central to tissue remodeling and NP formation in CRS. Dupilumab, as previously noted, is an anti-IL-4R α antibody and, as this subunit is utilized

by both the IL-4 and IL-13 receptors, the engagement of dupilumab blocks the activities of both cytokines. Dupilumab was initially approved for moderate to severe atopic dermatitis in 2017, and was later approved for moderate to severe asthma in 2018.

In 2019, dupilumab was FDA approved for CRSwNP as a result of two pivotal trials evaluating its use for CRSwNP when compared to intranasal steroids.²⁵ Co-primary endpoints included a reduction in nasal polyp score and improved nasal obstruction or congestion scores. Significant improvements were observed in both nasal polyp and congestion scores as well as in other measures of symptoms (total symptom score and SNOT-22). Dupilumab was also associated with remarkable improvements in olfaction and also in sinus severity as assessed by radiographic assessment (Lund-Mackay CT score) (Table 3). As a result of these findings, dupilumab became the first biologic treatment FDA approved for CRSwNP and can now be offered to patients failing conventional therapy.

Summary

Allergic rhinitis (AR), most presentations of nasal polyposis (NP), and many presentations of chronic rhinosinusitis (CRS) are type 2^{high} inflammatory diseases of the upper airway characterized by expression of the interleukins IL-4, IL-5, and IL-13 and infiltration with an allergic inflammatory state with eosinophils, mast cells, basophils, and many other inflammatory cells. Allergic rhinitis mediated in large part by IgE directed against aeroallergens. Strong evidence exists for a role for IgE in contributing to the presence and severity of CRSwNPs, although the target of this IgE is less clear and may not involve aeroallergens. Given the immune basis for these conditions a strong theoretical basis exists for targeting these conditions with biologics that neutralize IgE (omalizumab), IL-5 (mepolizumab, reslizumab), the IL-5 receptor (benralizumab), or both IL-4 and IL-13 (dupilumab). For many of these agents, compelling clinical studies support their use in AR or NP and, indeed, one of these biologics (dupilumab) has recently received FDA approval for use in NPs. However, these agents can be extremely expensive especially when considering the chronicity of these conditions and the likelihood that life-long therapy may prove warranted. Current therapies include combinations of medical therapies with nasal saline irrigation, antibiotics as appropriate, and combinations of topical and systemic corticosteroids. In many cases these approaches can provide long-term benefit and all – including surgery – are profoundly less expensive than biologics. Thus, future studies are imperative to address the cost effectiveness of biologics in these disorders, weighing in the adverse impact of these conditions on quality of life and determining their proper placement in therapy.

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Key Points

- Allergic rhinitis, most presentations of nasal polyposis (NP), and many presentations of chronic rhinosinusitis (CRS) are Type 2^{high} (interleukin (IL)-4^{high}, IL-5^{high}, IL-13^{high}) inflammatory diseases of the upper airway.
- Allergic rhinitis is mediated in large part by IgE and responds to IgE-targeting biologics
- Efficacy of biologics in CRS without nasal polyposis is theoretically plausible but no efficacy studies have been performed.
- Biologics that target IgE, IL-5, and the IL-4 receptor (the receptor for IL-4 and IL-13) have all demonstrated efficacy in the treatment of NP.
- Studies are essential to evaluate the cost effectiveness of biologics in these disorders and their proper placement in therapy in comparison to available medical and surgical therapies.

Clinics Care Points

- Allergic rhinitis is mediated in large part by IgE and responds to IgE-targeting biologics (omalizumab).
- Efficacy of biologics in CRS without nasal polyposis is theoretically plausible but no efficacy studies have been performed.
- Biologics that target IgE, IL-5/IL-5 receptors, and the IL-4 receptor have all demonstrated efficacy in the treatment of NP.
- Currently dupilumab is the only biologic having FDA approval for the treatment of NPs.
- Future studies are essential to evaluate the cost effectiveness of biologics in the treatment of these disorders and their proper placement in therapy in comparison to medical and surgical therapies.

Synopsis

Allergic rhinitis (AR), most presentations of nasal polyposis (NP), and many presentations of chronic rhinosinusitis are Type 2^{high} disorders characterized by expression of interleukins (IL) IL-4, IL-5, and IL-13. Neutralization of IgE with anti-IgE (omalizumab) has proven efficacy in AR. Similarly, in addition to anti-IgE, blockade of IL-5/IL-5 (mepolizumab, reslizumab, benralizumab), and dual blockade of IL-4 and IL-13 with anti-IL-4R (dupilumab) have demonstrated efficacy in NP. However, these agents are extremely expensive and future studies are essential to evaluate their cost effectiveness in comparison to current medical and surgical therapies.

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Table 1:

Meta-Analysis of Randomized Controlled of Omalizumab in Allergic Rhinitis

Parameter	Standardized Mean Difference (SMD)/ Relative Risk (RR)	p-value
Daily nasal symptom score	−0.443 (SMD)	p<0.001
Daily ocular symptom score	−0.385 (SMD)	p<0.001
Daily nasal medication symptom score	−0.421 (SMD)	p<0.001
Proportion of days with emergency drug use	0.418 (RR)	p<0.005
Rhinoconjunctivitis-specific qol questionnaires	−0.286 (SMD)	p<0.001
Overall evaluation	1.435 (RR)	p<0.001

Table 2:

Omalizumab Efficacy in Nasal Polyposis

Parameter	Mean Change (Polyp 1 / Polyp 2 study*)	p-value (Polyp 1 / Polyp 2 study)
Nasal congestion score	−0.89 / −0.70	0.0004 / 0.0017
Nasal polyp score	−1.08 / −0.90	<0.0001 / 0.014
SNOT-22** (0–110)	−24.70 / −21.59	<0.0001 / <0.0001
Sense of smell score (0–3)	−0.56 / −0.58	0.0161 / 0.0024
Total nasal symptom score (0–12)	−2.97 / −2.53	0.0001 / <0.0001
UPSIT** smell assessment (0–40)	4.44 / 4.31	0.0024 / 0.0011

* Polyp 1 study n=138; Polyp 2 study n=127.

** SNOT - Sinonasal outcome test; UPSIT - University of Pennsylvania Smell Identification Test

Table 3:

Dupilumab Efficacy in Nasal Polyposis

Parameter	Least squared mean change from baseline (SINUS-24 / SINUS-52 Trial [*])	p-value (SINUS-24 / SINUS-52 Trial)
Nasal polyp score (0–8)	–2.06 / –1.80	<0.0001 / <0.0001
Nasal congestion or obstruction score (0–3)	–0.89 / –0.87	<0.0001 / <0.0001
Lund-Mackay CT score (0–24)	–7.44 / –5.13	<0.0001 / <0.0001
Total symptom score (0–9)	–2.61 / –2.44	<0.0001 / <0.0001
UPSIT smell assessment (0–40)	10.56 / 10.52	<0.0001 / <0.0001
Loss of smell score (0–3)	–1.12 / –0.98	<0.0001 / <0.0001
SNOT-22 (0–110)	–21.12 / –17.36	<0.0001 / <0.0001

^{*} SINUS-24 study n=276; SINUS-52 study n=448