

The Role of Biologics in the Treatment of Nasal Polyps

Christine B. Franzese, MD

KEYWORDS

- Nasal polyposis • Chronic rhinosinusitis • Biologic • Omalizumab • Dupilumab
- Reslizumab • Mepolizumab • Benralizumab

KEY POINTS

- Chronic sinusitis with nasal polyposis (CRSwNP) is a heterogenous disorder with multiple endotypes and various treatment options, including both surgical and medical therapies.
- CRSwNP manifests as a chronic inflammatory condition and should be viewed as a disease of exacerbations that should be controlled through intervention, rather than a disease of surgical and/or medical “failures.”
- There are several biological agents that are either Food and Drug Administration–approved, completed Phase III trials with positive results, or are currently undergoing investigation for the treatment of CRSwNP.
- The role of biological agents in the treatment of CRSwNP as well as potential patient candidate characteristics for use are discussed.

INTRODUCTION

Where biological agents fit into current guidelines for the treatment of patients with chronic rhinosinusitis with nasal polyps (CRSwNP) is not as simple and straightforward as it has been with other interventions developed to treat the disease state. With the advent of any new medical or surgical intervention, when discussing where a particular treatment should fit into a therapeutic algorithm, consideration is generally given to the specific details of its usage: what its indications are, what type of patient would most benefit from it, and how to use it in actual clinical practice. Organizations (and individuals) may deliberate the further implications of where the new therapeutic option fits into currently available guidelines and its costs to the health care system, among other considerations. This scenario is complicated by the fact that chronic sinusitis with nasal polyposis [CRSwNP] is a heterogeneous disorder that is not completely understood and has different phenotypic endotypes that may or may not be associated with other systemic disorders.¹ The clinical implications of endotype designation on

Department of Otolaryngology–Head and Neck Surgery, University of Missouri-Columbia, One Hospital Drive, Suite MA314, Columbia, MO 65212, USA

E-mail address: franzesec@health.missouri.edu

Immunol Allergy Clin N Am ■ (2020) ■–■

<https://doi.org/10.1016/j.iac.2019.12.006>

0889-8561/20/© 2019 Elsevier Inc. All rights reserved.

immunology.theclinics.com

treatment is also not fully appreciated and options for treatment of CRSwNP include surgical and medical interventions that may vary in success, availability, and expense.²

Although only one biologic at present has Food and Drug Administration (FDA) approval for the treatment of CRSwNP,³ a second has recently announced positive results from its Phase III trials,⁴ and still more have ongoing Phase I, II, and III trials. Thus, it would be prudent to assume that one or more additional biologics will also receive FDA approval and to adapt current treatment parameters to accommodate these new therapeutic options for suitable patient candidates in a proactive manner. Indeed, the European Forum for Allergy and Airway Diseases published a consensus statement on the use of biologics for CRSwNP with or without asthma before any biologics receiving FDA approval for such usage.⁵ Other societies, groups, and organizations either have drafted or are in the process of drafting similar statements, updates, and/or guidelines to weigh in on what is appropriate usage and to prevent misuse/overusage.

Part of the challenge is that the understanding of the different types of inflammation driving the development of CRSwNP and its various clinical presentations is continually evolving.⁶ At present, 3 different types of inflammation (Type 1, Type 2, and Type 3) have been described.^{6,7} Type 1 inflammation is characterized by neutrophilic inflammation, T_H1 cells, and driven by interleukin (IL)-2, interferon γ , and tumor necrosis factor alpha (TNF- α). Type 2 inflammation is characterized by eosinophilic inflammation, T_H2 cells, and driven by IL-4, IL-5, IL-10, and IL-13. Type 3 inflammation is characterized by tissue fibrosis, T_H17 cells, and driven by IL-6, IL-17, IL-22, and TNF- α . Type 2 inflammation tends to be the dominant form of inflammation in CRSwNP in Western countries and the current biological therapies either approved for or under investigation for CRSwNP target aspects of Type 2 inflammation.^{1,6,7} Even with specific targeted therapy, the wide-ranging effects of these agents, the scarcity of published data, and their cost make the placement of biological agents in guidelines difficult.

Indeed, use of these biological agents entails significant expense, and due to financial factors alone, there is temptation to simply earmark biologics as a “treatment of last resort” to be used when all other measures have been exhausted or failed, and administering biologics before that is shameful overuse. However, such a designation would do a grave disservice to patients, as, unlike the question of where biologics fit into guidelines or algorithms, the role that biologics should play in the treatment of CRSwNP is more clear.

Similar to other Type 2 inflammatory disorders such as eosinophilic asthma, CRSwNP is a chronic inflammatory disease state where patients suffer from exacerbations and defining it as such can be helpful in determining the role these agents play. However, rather than episodes of wheezing, coughing, and chest tightness, patients with CRSwNP experience increased nasal congestion, polyp growth, decrease or loss of sense of smell, etc. as their exacerbations. It should not be viewed as “surgery has failed” or “medications have failed” but rather exacerbations that are either controlled with appropriate surgical and medical therapies or remain uncontrolled despite those treatments. Once the perception of CRSwNP is altered to a disease of chronic inflammation with the need to control exacerbations, the way treatment is viewed can be altered from a flow diagram type or algorithm type strategy to more of a step-wise strategy, similar to asthma. Criteria to designate asthma status as mild to severe and its control are assessed at each visit. Recommendations for controller medications then are categorized in a stepwise fashion with each particular category corresponding to one or more “steps.” Each step lists appropriate

medications/interventions with recommendations on additional measures for exacerbations or poor control. Treatment algorithms for CRSwNP could follow a similar fashion, establishing criteria for disease severity and accounting for different endotypes, while then designating “step” type therapy and determining on which step/disease severity biological agents should be placed.

Regardless of placement, the goal of initiating biological agents should be to improve exacerbation control in those uncontrolled patients, who would generally get further surgery or repeated high-dose and/or long-term oral corticosteroids. Oral corticosteroid use is a mainstay of therapy but has associated significant risks, particularly when used long term or at high dose.⁸ In patients who have had at least one surgery for CRSwNP, the role of biologics should be to reduce or eliminate the need for additional surgical interventions and additional courses of oral corticosteroids and/or antibiotics. In patients with CRSwNP who refuse surgery or are not surgical candidates due to comorbidities, the role of biologics should be to reduce or eliminate the need for repeated additional courses of oral corticosteroids and/or antibiotics once standard treatments have been attempted and either failed or could not be tolerated.

Keeping the role of biologics in mind and given that there are multiple points in current guidelines where these agents could fit, it may instead make more sense to define or identify those characteristics that make patients suitable candidates for biological agents, as their use is not appropriate in all patients. All of the commercially available biological agents are recombinant humanized monoclonal immunoglobulins that target a specific receptor, immunoglobulin, or cytokine-producing inhibitory downstream effects on binding. **Table 1** lists the commercially available biologics approved for, have some data available for, or are under investigation for the treatment of CRSwNP, each targeting a different immunologic aspect involved in the pathogenesis of CRSwNP. Agents not currently commercially available but under investigation for CRSwNP are listed in **Table 2**. The following is a brief review of biological agents, listed by what each agent targets. Once familiar with these agents and their mechanisms, suggestions as to what types of patient characteristics make one a suitable candidate for use can be further discussed.

Target: Interleukin 4/Interleukin 13

IL-4 is responsible for inducing the differentiation of naïve T cells into Th2 cells and isotype switching of B cells into IgE-producing plasma cells, among other effects. IL-13 regulates several immune processes including IgE synthesis, mucous hypersecretion, and fibrosis.

Table 1

Commercially available biological agents under investigation for chronic rhinosinusitis with nasal polyps

Name	Target	Status for CRSwNP	Dose
Dupilumab	IL-4 α subunit	FDA approved	300 mg SQ every 2 wk
Omalizumab	IgE	Phase III completed	150 mg/300 mg every 4 wk
Mepolizumab	IL-5	Phase III ongoing	100 mg SQ every 4 wk
Reslizumab	IL-5	Unknown	3 mg/kg IV infusion every 4 wk
Benralizumab	IL-5 receptor	Phase III ongoing	30 mg SQ every 4 wk X 3, then every 8 wk

Table 2

Noncommercially available biological agents under investigation for chronic rhinosinusitis with nasal polyps

Name	Target	Status	Dose
GB001	DP2 agonist	Phase 2a	Unknown daily dose
PF-06817024	IL-33	Phase 1	Various IV, SC doses
ACT-774312	CRTH2 receptor antagonist	Phase 2	Oral twice daily dose
Etokimab	IL-33	Phase 2a	SC dose every 4–8 wk
Fevipirant	CRTH2 antagonist	Phase 3	Oral daily dose

Information available at clinicaltrials.gov.

Abbreviations: IV, intravenous; SC, subcutaneous.

Agent: dupilumab (Dupixent)

This antibody functions as an IL-4 receptor α -subunit antagonist.³ Because the IL-4 receptor α -subunit is present in both Type I receptors that bind IL-4 and Type II receptors that bind IL-4 and IL-13, it modulates the effects of both cytokines. It is currently approved as an add-on maintenance treatment in adult patients with inadequately controlled CRSwNP, as well as the treatment of patients 12 years or older with moderate to severe atopic dermatitis uncontrolled by topical treatments, moderate to severe asthma with eosinophilic phenotype, and/or oral corticosteroid-dependent asthma.³

It has completed 2 Phase III trials, SINUS-24 and SINUS-52, both meeting their primary endpoints.³ Dupilumab significantly improved nasal polyp score (−2.06), nasal congestion (−0.89), and SNOT-22 (−21.12) from baseline to week 24 (least square mean differences vs placebo) and reduced systemic oral corticosteroid use for nasal polyposis surgery.³

The dosing for dupilumab for CRSwNP is administered subcutaneously in a prefilled syringe at home or in the office. Unlike atopic dermatitis or asthma, there is no loading dose for CRNwNP. The dose is 300 mg, which is generally first given in the office, so that patient training on how to administer the medication can occur. Thereafter, it is 300 mg every 2 weeks subcutaneously given at home by the patient. Transient eosinophilia has been seen after initiation, as the inhibition of IL-4/IL-13 will cause a decrease in the migration of eosinophils into peripheral tissues faster than a decrease in the production and release of eosinophils.³

Target: immunoglobulin E

Immunoglobulin E is 1 of 5 classes of antibodies and is the immunoglobulin that classically participates in the pathophysiology of atopic disorders.

Agent: omalizumab (Xolair)

This antibody functions as an IgE antagonist. It binds to free-floating IgE, specifically to the C ϵ 3 domain. The C ϵ 3 domain is crucial to IgE binding to receptors on cell surfaces; by omalizumab complexing with this domain, it prevents serum IgE from attaching to the Fc ϵ R1 high-affinity IgE receptor and the CD23 receptor.⁹ This inhibits the release of inflammatory mediators and upregulates the replacement of Fc ϵ R1 high-affinity IgE receptors with Fc ϵ R2 low-affinity IgE receptors.⁹ Omalizumab cannot bind to or displace bound IgE nor can it bind to any IgE receptors itself, thus preventing omalizumab from triggering mediator release and anaphylaxis.

Omalizumab is currently indicated for the treatment of poorly or uncontrolled moderate to severe persistent asthma despite inhaled corticosteroids in patients 6 years of age and older with a positive skin test or specific IgE reactivity to a perennial allergen

and for chronic idiopathic urticaria in patients 12 years of age or older who remain symptomatic despite H1 antihistamine treatment.¹⁰ Omalizumab can be given subcutaneously either every 2 weeks or every 4 weeks, and its dosage depends on what indication it is administered for and can be affected by weight and IgE level before initiation. It comes in a prefilled syringe or a lyophilized powder that must be reconstituted.¹⁰ It must be administered in the office and recommendations are to monitor patient postadministration due to the risk of anaphylaxis.¹⁰

It has completed 2 Phase III trials, POLYP1 and POLYP2, both meeting their primary endpoints, but no published data regarding these trials are currently available.⁴ For these trials, omalizumab could be given either every 2 weeks or every 4 weeks. Before this, 2 smaller clinical trials had evaluated the use of omalizumab in the treatment CRSwNP with conflicting results.^{11,12}

Target: Interleukin 5

IL-5 is responsible for the regulation of eosinophil production, maturation, and survival as well as the growth and differentiation of B lymphocytes.

Agent: mepolizumab (Nucala)

This antibody functions as an IL-5 antagonist by binding to IL-5 and preventing that cytokine from binding to the IL-5 receptor α -subunit. Mepolizumab is currently indicated as add-on maintenance therapy for the treatment of patients with poorly controlled or uncontrolled severe asthma with an eosinophilic phenotype aged 6 years and older and adult patients with eosinophilic granulomatosis with polyangiitis (EGPA).¹³

The dose of mepolizumab depends on age and indication. The dose for asthma is 100 mg and the dose for EGPA is 300 mg. Regardless of indication, it is given subcutaneously every 4 weeks and comes in 3 forms: a lyophilized powder that must be reconstituted, a prefilled syringe, and a self-administered autoinjector. The prefilled syringe and the autoinjector are for patients 12 years and older and are administered at home. The reconstituted powder is administered in the office while the patient is observed for adverse reactions.

There are currently ongoing Phase III trials (SYNAPSE) involving mepolizumab in the treatment of CRSwNP.¹⁴ No published data regarding these trials are available yet. A smaller Phase II trial demonstrated a significant reduction in polyp size with concurrent reduction in peripheral eosinophil count but did not result in symptomatic improvement.¹⁵

Agent: reslizumab (Cinqair)

This antibody also functions as an IL-5 antagonist by binding to IL-5 and preventing that cytokine from binding to the IL-5 receptor α -subunit. Reslizumab is currently indicated as add-on maintenance therapy for adult patients with poorly or uncontrolled severe asthma with an eosinophilic phenotype.¹⁶ The dosage is 3 mg/kg administered by intravenous infusion over 20 to 50 minutes every 4 weeks. It must be administered in the office and recommendations are to monitor patient postadministration due to the risk of anaphylaxis.

A reduction in nasal polyp size had been shown in a small, controlled trial of 8 patients using a single dose of 1 mg/kg of reslizumab.¹⁷ A phase III trial involving reslizumab in the treatment of CRSwNP was listed on clinicaltrials.gov but no longer seems to be available.

Agent: benralizumab (Fasenra) Although this agent does affect IL-5, it is different from the prior 2 as benralizumab actually binds to the IL-5 receptor itself. The monoclonal antibody is engineered without a fucose molecule, and thus upon binding to the IL-5

receptor, can trigger antibody-dependent cell cytotoxicity and apoptosis in eosinophils and mast cells. Benralizumab is currently indicated as add-on maintenance therapy for the treatment of patients with poorly controlled or uncontrolled severe asthma with an eosinophilic phenotype aged 12 years and older.¹⁷ It has also been granted orphan drug status for adult patients with EGPA.^{18,19}

It comes in a prefilled syringe and the dosage is 30 mg every 4 weeks for the first 12 weeks, then every 8 weeks thereafter. It must be administered in the office and recommendations are to monitor the patient postadministration.

There are currently ongoing Phase III trials (OSTRO) involving benralizumab in the treatment of CRSwNP,²⁰ as well as an open-label study (BITE) for the treatment of EGPA.²¹ No published data regarding these trials are available yet.

BIOLOGICS: WHERE DO THEY FIT IN CLINICAL PRACTICE?

Keeping in mind the goal of using biological agents to control exacerbations without the need for additional courses of oral corticosteroids, antibiotics, or surgery in patients with CRSwNP helps with the identification of characteristics of patient candidates where these agents may be helpful. It is also important to keep in mind that no therapy is 100% successful and that many candidates do quite well after functional endoscopic sinus surgery (FESS) with continued medical management. In addition, the goals and desires of the patient should be elicited as part of shared decision-making process, so that recommendations for treatment are tailored to suit the needs of the individual.

Box 1 is the author's opinion of potential characteristics of patients who could be suitable candidates for initiation of a biological agent, given the following assumptions:

1. The patient suffers from significant symptoms consistent with the diagnosis of CRSwNP such as nasal obstruction and loss of sense of smell
2. Has endoscopic and/or computed tomographic scan findings consistent with CRSwNP and has had appropriate medical treatment²
3. Has had continued symptomatic polyp regrowth, despite appropriate surgical treatment and/or more than one course of high dose and/or long-term course of an oral corticosteroid in a 12-month period

Box 1

Some patient characteristics where a biological agent may be appropriate

Patient has symptomatic CRSwNP, despite appropriate medical/surgical therapy AND one or more of the following:

- Separately meets criteria for a second indication, such as chronic urticaria, asthma, etc.
- Has had one or more FESS with recurrence of symptomatic polyps in a short time frame (6 months or less) despite compliance with topical intranasal therapies
- Has had one or more FESS with recurrence of symptomatic polyps in a longer time frame (greater than 6 months) despite compliance with therapy but declines/refuses additional surgery
- Has contraindications or medical comorbidities such that additional courses of oral or types of corticosteroid therapy would be potentially harmful or contraindicated, such as uncontrolled or poorly controlled diabetes mellitus, osteoporosis or stress fractures, cataracts, etc.
- Declines/refuses surgery and has attempted appropriate medical management, including topical intranasal steroids, but has required more than one course of high dose and/or long-term oral corticosteroids in a 12-month period

This list is not meant to be an exhaustive enumeration of all potential characteristics, but as a guide to a starting point in the identification of possible candidates for this type of therapy.

At present, there are no Type 2 biomarkers that can definitely determine which biological treatment should be initiated or is right for the patient; however, they can serve as guides to the practitioner in selecting which one to initiate, if the patient is an appropriate candidate. The selection of which biologic to use for CRSwNP alone at this stage is a moot point, as the only FDA-approved biologic for the treatment of CRSwNP is dupilumab. If another biologic is desired for use, a separate indication for that particular agent would be required.

FUTURE CONSIDERATIONS/SUMMARY

Table 2 lists biological agents not commercially available but under investigation for nasal polyposis. Without doubt, one or more of these investigational or commercially available biologics will succeed in clinical trials and receive FDA approval for use. Adapting our practice patterns, considering appropriate patient characteristics, and using judicious caution in both the prevention of zealous overuse as well as the prevention of inappropriate restrictions will be helpful in enhancing the care and quality of life for our patients with CRSwNP. Rethinking the way CRSwNP is viewed to be more like an inflammatory condition with exacerbations that must be controlled, rather than disease of surgical or medical “failures,” could be helpful in finding the right fit of treatment algorithms for these therapies. Perhaps alteration of our treatment algorithms into more of a “step-wise” paradigm would aid in designating where these agents should fit. No doubt these therapies will alter the way practitioners treat CRSwNP but exactly how practice will change remains to be seen.

DISCLOSURE

Author has the following conflicts of interest: Speaker’s Bureau-ALK, GSK, AZ, Regeneron-Sanofi, Optinose; Advisory Board-ALK; Research funding-Merck, ALK, GSK, Novartis/Genetech/Roche, Optinose.

REFERENCES

1. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol* 2016;137(5):1449–56.e4.
2. Orlandi RR, Kingdom TT, Hwang PH, et al. International consensus statement on allergy and rhinology: rhinosinusitis executive summary. *Int Forum Allergy Rhinol* 2016;6(Suppl 1):S3–21.
3. Dupilumab package insert. Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761055lbl.pdf. Accessed August 30, 2019.
4. Xolair® (omalizumab) significantly reduced nasal polyps and congestion symptoms in adults with chronic rhinosinusitis with nasal polyps in two phase III studies. Available at: <https://www.biospace.com/article/releases/xolair-omalizumab-significantly-reduced-nasal-polyps-and-congestion-symptoms-in-adults-with-chronic-rhinosinusitis-with-nasal-polyps-in-two-phase-iii-studies>. Accessed August 20, 2019.
5. Fokkens WJ, Lund V, Bachert C, et al. EUFOREA consensus on biologics for CRSwNP with or without asthma. *Allergy* 2019. <https://doi.org/10.1111/all.13875>.

6. Stevens WW, Peters AT, Tan BK, et al. Associations between inflammatory endotypes and clinical presentations in Chronic Rhinosinusitis. *J Allergy Clin Immunol Pract* 2019. <https://doi.org/10.1016/j.jaip.2019.05.009>.
7. Smith KA, Pulsipher A, Gabrielsen DA, et al. Biologics in chronic rhinosinusitis: an update and thoughts for future directions. *Am J Rhinol Allergy* 2018;32(5): 412–23.
8. Poetker DM, Reh DD. A comprehensive review of the adverse effects of systemic corticosteroids. *Otolaryngol Clin North Am* 2010;43(4):753–68.
9. Johansson SGO, Haahtela T, O'Byrne M. Omalizumab and the immune system: an overview of preclinical and clinical data. *Ann Allergy Asthma Immunol* 2002; 89:132–8.
10. Omalizumab package insert. Available at: https://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed August 30, 2019.
11. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol* 2013;131:110–6.
12. Pinto JM, Mehta N, DiTineo M, et al. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinology* 2010;48(3):318–24.
13. Mepolizumab package insert. Available at: https://gsksource.com/pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL-IFU-COMBINED.PDF. Accessed August 30, 2019.
14. Effect of mepolizumab in severe bilateral nasal polyps. Available at: <https://clinicaltrials.gov/ct2/show/NCT03085797>. Accessed September 5, 2019.
15. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol* 2011;128(5):989–95.
16. Reslizumab package insert. Available at: <https://www.cinqair.com/globalassets/cinqair/prescribinginformation.pdf>. Accessed August 30, 2019.
17. Gevaert P, Lang-Loidolt D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol* 2006;118(5):1133–41.
18. Benralizumab package insert. Available at: <https://www.azpicentral.com/fasenra/fasenra.pdf#page=1>. Accessed August 30, 2019.
19. FDA Grants ODD to AstraZeneca's Fasenra to Treat EGPA. Available at: <https://www.pharmaceutical-technology.com/news/fda-grants-odd-for-astrazenecas-fasenra-to-treat-egpa>. Accessed September 5, 2019.
20. Efficacy and Safety Study of Benralizumab for Patients With Severe Nasal Polyposis (OSTRO). Available at: <https://clinicaltrials.gov/ct2/show/NCT03401229>. Accessed September 5, 2019.
21. Benralizumab in the Treatment of Eosinophilic Granulomatosis With Polyangiitis (EGPA) Study (BITE). Available at: <https://clinicaltrials.gov/ct2/show/NCT03010436>. Accessed September 5, 2019.