

Biologic Agents for the Treatment of Chronic Rhinosinusitis With Nasal Polyps

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Abstract

Background: Chronic rhinosinusitis with nasal polyposis is a complex inflammatory disorder, which is often recalcitrant to medical and surgical management. Recently, biologic agents have been studied as an adjunct treatment for this patient population.

Objective: The purpose of this study is to examine the role of biologic agents for chronic rhinosinusitis patients by reviewing literature and clinical trials.

Methods: A comprehensive review of literature and clinical trials—both recently completed and ongoing—was undertaken to examine up-to-date evidence of current biologic therapy and its role in chronic rhinosinusitis patients—including anti-IgE, anti-IL-4, anti-IL-5, anti-IL-13, and GATA-3 DNzyme.

Results: Specific biologic agents discussed include omalizumab, reslizumab, mepolizumab, benralizumab, dupilumab, and Hgd40/SB010. Risks, side effects, and administration information are also reviewed. An algorithm for the use of biologics in patients with chronic rhinosinusitis with nasal polyposis is proposed.

Conclusion: These treatments have promising results and may prove to be an important adjunct for patients with recalcitrant sinus disease.

Keywords

chronic rhinosinusitis, nasal polyposis, biologic agents, anti-IgE, anti-IL-4, anti-IL-5, anti-IL-13, GATA-3 DNzyme, omalizumab, reslizumab, mepolizumab, benralizumab, dupilumab, Hgd40, SB010

Introduction

Chronic rhinosinusitis (CRS) is a complex inflammatory disorder affecting approximately 10% of the population in the United States. It is a clinical syndrome with multiple phenotypes of the disease, which encompass different inflammatory and remodeling patterns. Chronic rhinosinusitis with nasal polyposis (CRSwNP) is considered a more severe form than chronic rhinosinusitis without nasal polyposis (CRSsNP). The presence of polyposis is most often characterized by local Th2 pathways involving eosinophilic inflammation and elevated levels of IL-5 and IgE.¹ It is theorized that polyps may develop secondary to the inflammatory reaction stimulated by the release of toxic materials from eosinophils.¹ However, noneosinophilic inflammation dominated by Th1 and Th17 pathways may also be seen resulting in varied cytokine profiles among patients with CRSwNP.² For instance, Cao et al. found that non-Caucasian

patients had polyps with less expression of IL-5 and eosinophils.^{2,3} CRSwNP is a more clinically severe form of rhinosinusitis especially when comorbid with asthma and can be recalcitrant to both medical and surgical management. Recently, biologic agents have been studied in clinical trials as an adjunct treatment for this patient population given demonstrated success in treating patients with asthma and atopic dermatitis.⁴ Meta-analysis has also shown promising data regarding the

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effect of IL-5 agents in reducing the number of nasal polyps in patients with CRSwNP as well as the effect of anti-IgE therapy in reducing the number of nasal polyps in patients with CRSwNP and concomitant asthma.⁴ This article aims to discuss up-to-date evidence of current biologic therapy and its role in CRS patients—including anti-IgE, anti-IL-4, IL-5, IL-13, and GA-TA-3 DNAzyme.

Current Basic Management

Current basic medical management for CRSwNP and CRSsNP varies slightly, based on the 2016 International Consensus Statement on Allergy and Rhinology, as CRSwNP is associated with an intense local eosinophilic inflammation with high IL-5 levels.

The mainstay of medical therapy for both phenotypes, with grade A evidence to support their usage, includes nasal saline irrigations and intranasal corticosteroid sprays for maintenance therapy and systemic corticosteroids with antibiotics for acute exacerbations.^{5,6} A brief course of oral corticosteroids and aspirin desensitization (for patients with aspirin-exacerbated respiratory disease) is only recommended in the treatment of patients with nasal polyps.⁷ Optional treatments include macrolide therapy for both CRSsNP and CRSwNP, whereas anti-leukotrienes have only been shown to benefit CRSwNP.^{8,9} Antibiotics are available for acute infectious exacerbations of baseline disease. If patients still do not experience symptom relief, endoscopic sinus surgery may be considered in order to alleviate obstruction, remove inflammatory tissue, and facilitate delivery of topical therapies.¹ Surgery is not considered curative; however, it provides improved access for future continued medical therapy.

Rate of success of current medical management of CRS is estimated to be at approximately 50%.¹⁰ Failure of medical and surgical management is more likely in certain phenotypes, including nasal polyposis, comorbid asthma, aspirin-exacerbated respiratory disease (AERD), allergic fungal rhinosinusitis (AFRS), and certain symptom profiles—including facial pressure/pain, mucosal inflammation, and higher endoscopic severity grade.¹¹

Recently, biologic agents targeted at IgE and other type 2 (Th2) pathways prevalent in patients with CRSwNP and asthma have been shown in randomized, double-blind studies to subjectively and objectively improve outcome measurements. Although not currently approved by the FDA for the treatment of CRSwNP, these therapies are approved for the treatment of asthma and atopic dermatitis (dupilumab). When used for those indications in the setting of comorbid CRSwNP, studies have shown successful and promising results. These therapies are discussed in detail below (Figure 1).

Anti-IgE Antibodies

Omalizumab is an anti-IgE monoclonal antibody which binds IgE's high affinity Fc receptor on a variety of inflammatory cells in blood and interstitial fluid, blocking the IgE-mediated inflammatory cascade and significantly reducing free IgE serum concentrations.¹² It also has a secondary effect resulting in the downregulation of the Fc receptor on basophils, mast cells, and dendritic cells leading to reduced release of mediators in addition to free IgE.¹³ This effect may take up to 16 weeks to completely take effect and will take a few months to wear off following medication discontinuation.¹³ This is clinically beneficial in patients with CRSwNP and comorbid asthma given the high incidence of eosinophil cationic protein, local IgE, and *Staphylococcus aureus* enterotoxin IgE in the nasal polyp tissue.¹⁴

Omalizumab has been approved by the FDA for treating moderate to severe asthma in patients aged 12 years and older whose symptoms are not controlled by inhaled corticosteroids (Table 1). It is contraindicated in patients who experience an anaphylactic reaction in response to treatment.¹⁵ Omalizumab is administered by subcutaneous injection every 2 to 4 weeks, with weight-based dosing. Dosing and frequency level is determined by serum total IgE level and body weight and is administered in clinic, due to a 0.2% risk of anaphylaxis.¹⁶ Previously, there were concerns that omalizumab was associated with malignancy; however, more recent data from the prospective cohort EXCELS trial suggest that this is not the case.¹⁷ In 2014, the FDA added cardiovascular risks to the label for omalizumab, as trials over the past decade were conflicting.¹⁸ More common reactions were upper respiratory tract infections, sinusitis, injection site reaction, headache, and pharyngitis.¹⁹

In a randomized, double-blind, placebo-controlled phase II trial, Gevaert et al. demonstrated a significant reduction in total endoscopic nasal polyp score (a measured scale grading polyp size, location, and degree of obstruction) and associated symptoms in allergic and nonallergic patients with nasal polyps and asthma.²⁰ A systematic review conducted by Tsetos et al. compared the results of the randomized clinical trial conducted by Gevaert et al. with Pinto et al. which explored the efficacy of omalizumab as an alternative therapeutic option in patients with CRSwNP and comorbid asthma.²¹ Clinical improvement was measured in both clinical trials through total polyp score (TPS), pre- versus post-treatment sinus opacification on computed tomography (CT) imaging, quality of life measures, and nasal airflow peak nasal inspiratory flow and olfaction (UPSIT). The clinical trial conducted by Pinto et al. did not find statistically significant changes in any of the aforementioned categories. The study conducted by Gevaert

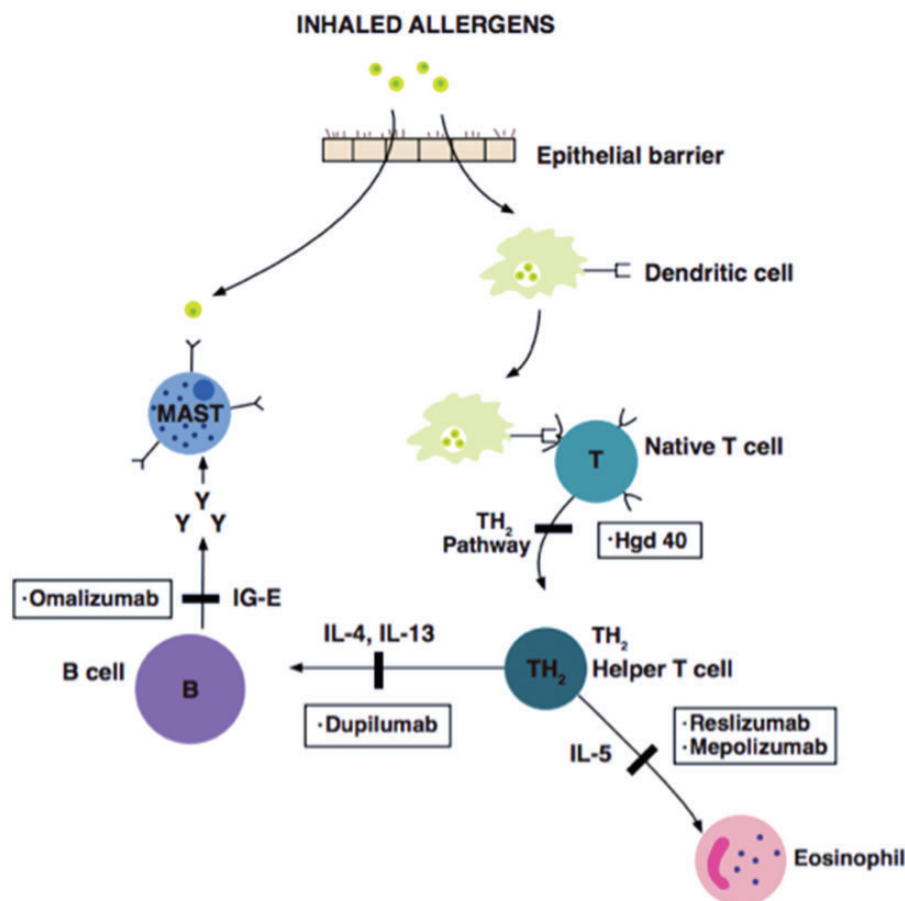


Figure 1. Diagram of the immunologic response to inhaled allergens, demonstrating the points at which relevant biologic agents inhibit the process. Used by permission—Julia E. Kartush, 2018.

et al., on the other hand, found significant improvement in all measurements, except for nasal airflow and olfaction.¹⁹ Although statistically significant improvements were only reported by 1 of the 2 clinical trials evaluated, systematic review supports the use of omalizumab as an alternative option in this patient population.¹³ It should also be noted that the study conducted by Gevaert et al. had some potential limitations including a limited number of participants (24) and higher baseline eosinophilic inflammation in the placebo-treated subjects, despite randomization. The placebo-arm of study also experienced a 50% dropout rate.¹⁹ The study conducted by Pinto et al. also noted limitations regarding the number of enrolled participants, highlighting the need for a trial with larger enrollment.²²

The effect of anti-IgE biologic therapy has also been explored in subsets of patients with AFRS, AERD, and eosinophilic granulomatosis with polyangiitis (EGPA). Omalizumab has found to be clinically beneficial in patients with moderate to severe asthma and comorbid AFRS.²³ Patients with AERD are also believed to benefit from this therapy; the study conducted by Gevaert et al.

included 24 patients with CRSwNP, half of which also had AERD. The subset of patients with AERD experienced improved airway symptoms and quality of life but did not show clear improvement on CT.¹⁹ Two case reports have also shown clinical improvement and loss of aspirin sensitivity in patients with AERD and severe asthma following omalizumab treatment.^{24,25} Observational reports have shown patients with EGPA to benefit from omalizumab therapy in the context of comorbid asthma and sinonasal disease. The mechanism of omalizumab does not target the underlying vasculitis contributing to EGPA pathophysiology. However, the secondary effect of omalizumab, which leads to indirect apoptosis of eosinophils, is believed to help improve clinical symptoms in patients with specific clinical manifestations.²⁶ A retrospective review of 17 patients with asthma and refractory or relapsing EGPA treated with omalizumab experienced a decrease in prednisone dosage to less than 7.5 mg/day but did not show a decrease in mean eosinophil levels.²⁶ A case report also describes a patient with EGPA and refractory asthma whose asthma control ultimately improved on omalizumab therapy.²⁷

Anti IL-5 Antibodies

Activated Th2 cells synthesize and release cytokines, including IL-4, IL-5, and IL-13, which are involved in increased local production of IgE.²⁸ IL-5 is a key driver of eosinophilia, chemotaxis, differentiation, activation, and eosinophil survival.¹³ Preventing IL-5 from binding to the IL-5R subunit α (IL-5Ra) on the surface of eosinophils is a promising therapeutic strategy as IL-5 has been shown to be prominent in 80% of nasal polyps in certain populations. Furthermore, these agents also exhibit a secondary effect through eliminating eosinophils in circulation and within tissue, further enhancing therapeutic benefit. The following therapies target cytokines in this pathway.

Reslizumab is an anti-IL-5 monoclonal antibody that binds to IL-5, preventing it from binding the α subunit of the IL-5 receptor. The FDA approved its use in March 2016 for use with other asthma medications for maintenance treatment of severe eosinophilic asthma in patients aged 18 years and older. Administration is by IV infusion over 30 min, and dosage regimen is 3 mg/kg once every 4 weeks.²⁹ Patients with asthma who were found to be most responsive to treatment typically had a peripheral blood eosinophil level of greater than 400 cells/mcL.²⁹ The most common side effects are oropharyngeal pain, increased blood creatine phosphokinase, and myalgias.³⁰ In a randomized, double-blind, placebo-controlled trial, Gevaert et al. evaluated the effects of a single 1 mg/kg injection of reslizumab on 8 patients with nasal polyposis. The medication was safe and well tolerated; with 5 of the 8 total patients showing improvement in TPS for up to 12 weeks.³¹ Half of the patients who received a 3 mg/kg infusion experienced a reduction in TPS for 4 weeks.³¹ Elevated local nasal IL-5 levels at baseline, versus systemic levels, were predictive of a positive response to reslizumab. Further analysis suggested that basing patient selection on nasal IL-5 levels would improve outcomes in future studies.

Mepolizumab is an anti-IL-5 monoclonal antibody with the same mechanism of action as reslizumab. It was FDA approved in 2015 for maintenance treatment of severe eosinophilic asthma refractory to inhaled corticosteroids in patients aged 12 years and older. It also has been approved to treat EGPA. Patients with asthma that are most responsive have been shown to have peripheral blood eosinophil levels greater than 150 cells/mcL.³² Mepolizumab is administered as a standard dose of 100 mg monthly subcutaneous injections regardless of weight.³³ The most common side effect in clinical trials was headache, followed by injection site reaction, back pain, and fatigue.³⁴ In a randomized, double-blind study, Gevaert et al. studied patients with chronic sinusitis with severe nasal polyposis refractory to corticosteroid therapy, who received either 2 injections of

mepolizumab or placebo. The results showed a statistically significant reduction in endoscopic nasal polyp score and CT scans. Of note, this study included a subset of patients with AERD; however, it was unclear how many patients had a confirmed diagnosis and the specific additional benefit of mepolizumab in the treatment of AERD remains unclear.³⁰ Symptoms of CRSwNP trended toward improvement but did not reach significance. The authors noted that a major study limitation was its smaller sample size of 30, and the lack of symptom improvement could likely be attributed to this reason.³⁰ In a randomized, double-blind, placebo-controlled trial conducted by Bachert et al., patients with recurrent nasal polyposis requiring surgery were either given 750 mg of mepolizumab or placebo every 4 weeks for a total of 6 doses in addition to daily topical corticosteroids.³⁵ The primary outcome measure was whether or not patients still required surgery at the end of the 25 week period.³⁵ The study found that a statistically significant number of patients in the mepolizumab group did not require surgery as compared to the placebo group.³⁵ The authors noted that the study was limited in the length of treatment period, and it is possible that greater clinical improvement may be seen with longer courses of treatment.³⁵ In both clinical trials mentioned, mepolizumab was safe and well tolerated.^{30,35} Of note, there was no reactive eosinophilia, which has been observed with reslizumab.³⁰

Benralizumab is an anti-IL-5 monoclonal antibody which binds to the α chain of the IL-5 receptor initiating a direct, rapid depletion of eosinophils through enhancing the antibody-dependent cell-mediated cytotoxic pathway with the assistance of natural killer cells.³⁶ A secondary effect results in eosinophils dying off within 24 h.³⁶ Benralizumab was approved in November 2017 for add on maintenance of severe eosinophilic asthma in patients aged 12 years and older;³⁷ 30 mg is administered via subcutaneous injection once every 4 weeks for the first 3 doses, then subsequently once every 8 weeks.³⁶ Patients most responsive to treatment have peripheral blood eosinophil levels greater than 300 cells/mcL.³⁶ Side effects include headache, pharyngitis, and injection site reactions. A phase II, double-blind, randomized, placebo-controlled trial is currently ongoing, evaluating the efficacy of benralizumab on eosinophilic rhinosinusitis.³⁸

Anti IL-4/IL-13 Antibodies

Dupilumab is an anti-IL-4 monoclonal antibody which functions by targeting the α chain of IL-4Ra, a common receptor for both IL-4 and IL-13. These 2 cytokines play a prominent role in the Th2 pathway and pathogenesis of nasal polyp formation.¹³ IL-13 has multiple effects in asthma and may have a similar role

involving chemokine induction in CRS.³⁹ Dupilumab was approved in 2017 to treat adults (age 18+ years) with moderate to severe atopic dermatitis. It has also demonstrated efficacy in treating asthma although has not yet been approved for this indication.^{40,41} Dupilumab is administered via subcutaneous injection, with an initial dose of 600 mg, followed by 300 mg every other week.⁴¹ The most common adverse effects were nasopharyngitis, injection site reaction, and headache. A randomized, double-blind, placebo-controlled study was conducted on patients with CRSwNP, with or without concomitant asthma, refractory to intranasal corticosteroids. Patients in the experimental group were given a loading dose of subcutaneous dupilumab, followed by weekly dosing. Dupilumab treatment was associated with significant improvements in clinical, endoscopic, radiographic, and pharmacodynamic end points, and improvement in quality of life. It was also the only monoclonal antibody shown to significantly improve olfaction as measured by UPSIT (University of Pennsylvania Smell Identification Test) score.¹³ Dupilumab was safe and well tolerated. As compared to the anti-IL-5 antibodies, dupilumab does not have a secondary mechanistic effect and has shown rapid loss of therapeutic benefit with discontinuation or interrupted administration.⁴¹

GATA-3 Suppression

Hgd40 is a GATA-3 DNzyme, which is a novel therapy that targets an upstream transcription factor of the Th2 inflammatory pathway. GATA-3 is considered the “master-switch” of disease associated with this particular pathway and is overexpressed in patients with nasal polyps, asthma, and atopic dermatitis.⁴² This DNA enzyme was developed to enter T cells and use a catalytic enzyme to reduce the expression of GATA-3 RNA and subsequently decrease Th2 reactions.⁴³ In a randomized, double-blind, placebo-controlled trial, an inhaled form of Hgd40—SB010—significantly decreased early and late asthmatic responses in patients with allergic asthma, and as well as markers associated with Th2-regulated inflammation. Phase I and II trials have been completed on patients with asthma and atopic dermatitis, in the past several years.⁴⁴ This enzyme has high potential for the future treatment of other disease regulated by this pathway, including nasal polyposis.

Discussion

CRS is a complex disease, with certain phenotypes and endotypes experiencing greater failure in medical and surgical therapies. Biologic agents may offer supplemental therapy for patients with CRSwNP, by inhibiting the inflammatory pathway associated with nasal polyposis.

In the authors' opinion, informed consent for use of these biologics should be based on known data from clinical trials. All risks, benefits, and alternatives should be presented as thoroughly as possible. The potential for improvement in symptoms; yet, the limited and newer use of these medications should be fully disclosed.

Patients with CRSwNP may express various Th1, Th2, or Th17 cytokine profiles that can help guide individualized therapeutic regimens.² Identification of biomarkers aid in precise phenotyping and facilitate the targeting of specific biologic mechanisms underlying the diseases process. This has proven beneficial in the management of severe refractory asthma. In this context, the presence of biologic markers such as blood eosinophil levels, periostin, ANCA, and IL-5R levels help to identify the most appropriate biologic agent to effectively target an individual's inflammatory cascade.⁴⁵ For example, asthmatic patients treated with lebrikizumab, an anti-IL-13 monoclonal, had greater response rates (improvement in forced expiratory volume in 1 second rates) in the setting of higher serum levels of periostin.³⁹ In the literature, periostin has been found associated with CRSwNP, IgE, anti-staphylococcal IgE, CRS with asthma, and AERD.^{46,47} Thus, this biomarker may be helpful in identifying patients with CRSwNP who would be more responsive to anti-IL-13 agents. It is becoming more evident that an individualized approach involving these biomarkers will likely be necessary for both clinical improvement and cost-effectiveness in the future.

Although, at this time, these therapies are only approved to treat other inflammatory pathologies, many trials are showing subjective and objective improvements in patients with CRSwNP as well as a good safety profile. The exact application of these biologics will continue to evolve. Combinations of biologic therapies are already being explored. A number of case studies have reported findings associated with the combination of omalizumab and mepolizumab treatment in severe cases of refractory asthma.^{48,49} Patient steroid regimens were able to be steadily decreased with the addition of mepolizumab injections to omalizumab therapy.⁴⁸ It should also be noted that prior treatment with omalizumab has been shown to not preclude therapeutic response to mepolizumab in 2 randomized double-blind, placebo-controlled trials.⁵⁰ Patients in the trials responded positively to mepolizumab regardless of history of omalizumab treatment.⁵⁰ Therapies directed at other cytokines such as thymic stromal lymphopoietin (TSLP) are also currently being studied. TSLP is expressed by epithelial cells at the barrier of respiratory epithelium and is released in response to various insults such as allergens, smoke, or viruses.³⁹ It has been reported by Buchheit et al. that TSLP plays a role in

the inflammatory cascade of AERD through driving prostaglandin D₂ production from mast cells. It has also been found in increased levels in polyp tissue in these patients.⁵¹ Given its role in mediating inflammation, Tezepelumab, an anti-TSLP monoclonal antibody, is currently being studied in clinical trials for asthma and atopic dermatitis. Thus far, it has had significant effect in reducing asthma exacerbations as well as decreasing peripheral eosinophil counts and serum

IgE levels.³⁹ Due to these effects, this therapy may also have an important future implications for treating recalcitrant CRSwNP in which elevated eosinophils and IgE is also present.

The authors have included a proposed algorithm to suggest the timing for the evaluation and treatment with biologics within a commonly used workflow for CRS patients (Figure 2). The possible indications as they could relate to CRS patients have yet to be developed.

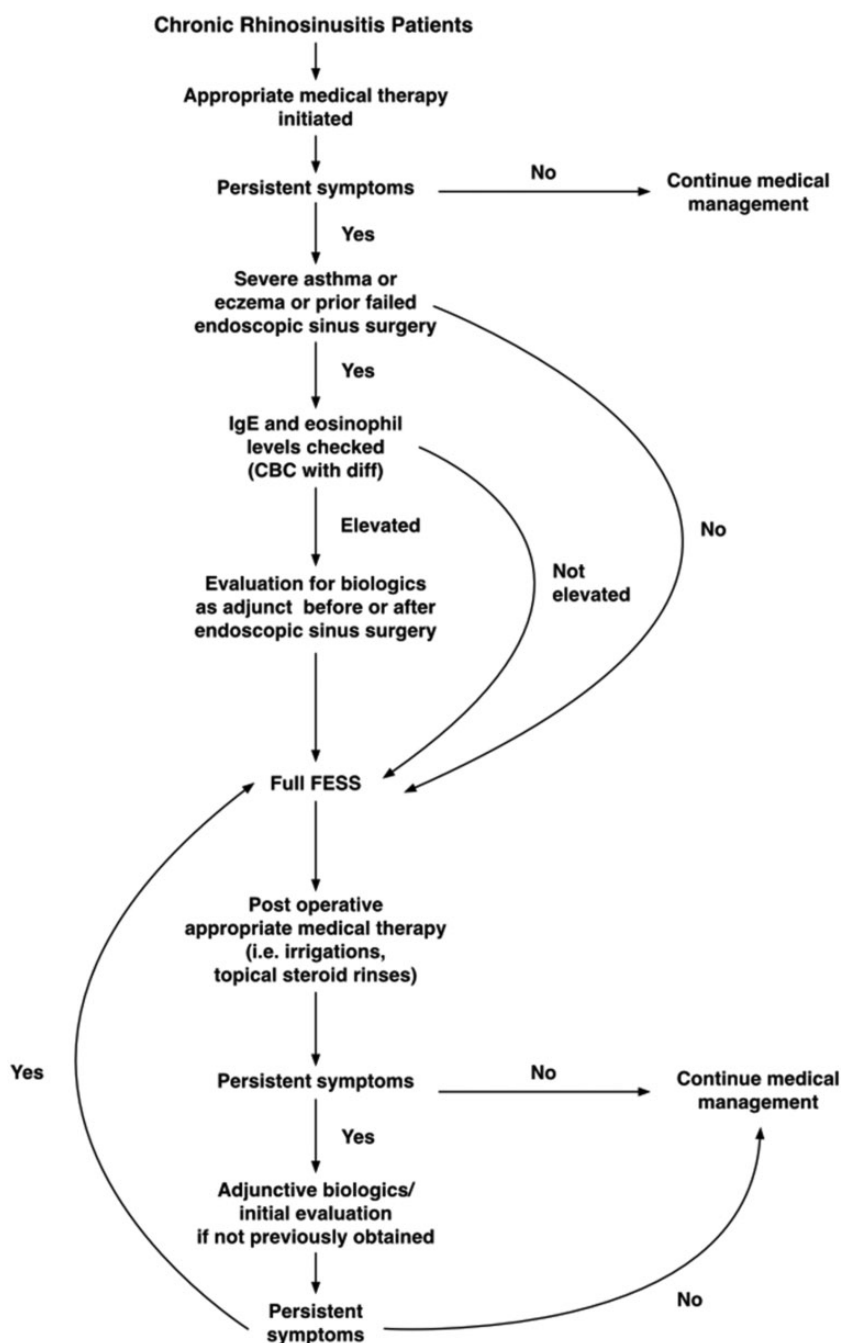


Figure 2. Algorithm proposed by the authors to suggest the timing for the evaluation and treatment with biologics within a commonly used workflow for chronic rhinosinusitis patients. Used by permission—Julia E. Kartush, 2018. CBC: complete blood count; FESS: functional endoscopic sinus surgery.

Table 1. Table Describing Biologic Agents Discussed With Mechanism, Route of Administration, and Side Effects Described.

Generic Name	Brand Name	Mechanism	Route of Administration	Side Effects
Omalizumab	Xolair	1. Binds to free IgE 2. Down regulates FcεRI 3. Decreased mediator release	Subcutaneous injection every 2–4 weeks Dosing and frequency level is determined by serum total IgE level and body weight	• Upper respiratory tract infections • Sinusitis • Headache • Pharyngitis • Cardiovascular risks • 0.2% risk of anaphylaxis • Injection site reaction
Mepolizumab	Nucala	1. Binds to IL-5 2. Inhibits production and survival of eosinophils	100 mg monthly subcutaneous injections regardless of weight	• Headache • Back pain • Fatigue • Injection site reaction
Reslizumab	Cinqair	1. Binds to IL-5 2. Inhibits production and survival of eosinophils	IV infusion over 30 min Dosage regimen 3 mg/kg once every 4 weeks	• Oropharyngeal pain • Increased blood creatine phosphokinase • Myalgias
Benralizumab	Fasenra	1. Binds to IL-5Rα 2. Inhibits production and survival of eosinophils	Subcutaneous injection 30 mg once every 4 weeks for the first 3 doses, then subsequently once every 8 weeks	• Headache • Pharyngitis • Injection site reaction
Dupilumab	Dupixent	1. Binds to IL4Rα, thereby inhibiting signaling of IL-4 and IL-13	Subcutaneous injection, with an initial dose of 600 mg, followed by 300 mg every other week	• Nasopharyngitis • Headache • Injection site reaction

More specifically, the use of these medications preoperatively versus postoperatively, duration of therapy, use in revision cases, and possible future phenotyping is yet to be determined. The question of the cost-effectiveness also remains an important factor that has yet to be fully addressed. As it pertains to the treatment of asthma and atopic dermatitis, 2 studies have shown that the benefit of treatment with omalizumab and dupilumab outweighs the cost.¹³ A health economic model was developed by Kuznik et al. which found dupilumab to be cost-effective for the treatment of atopic dermatitis at annual price of maintenance therapy in the range of \$29,000 to \$40,000 at the \$100,000 to \$150,000 per quality-adjusted life-year (QALY) thresholds.⁵² In regard to the treatment of asthma, Whittington et al. developed a Markov model which determined the cost per QALY gained for mepolizumab plus standard of care versus standard of care alone to be estimated at \$386,000 per QALY.¹ According to the authors, the cost of mepolizumab would require a 60% reduction in order to achieve cost-effectiveness of approximately \$150,000 per QALY.⁵¹ Thus, in terms of using monoclonal antibodies in the management of patients with CRSwNP, the cost-effectiveness of these agents must be further evaluated prior to implementation.¹³ The potential savings resulting from reduced need for

additional revision endoscopic sinus surgery should also be considered in a cost analysis. In conclusion, with further study, biologic agents may prove to be a very important and useful adjunct for patients with recalcitrant sinus disease.

Declaration of Conflicting Interests

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