Biologic Therapy for the Treatment of Chronic Rhinosinusitis with Nasal Polyposis: An Update and Review of the Literature

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Abstract

Chronic rhinosinusitis (CRS) is a common inflammatory syndrome of the paranasal sinuses. CRS with nasal polyposis (CRSsNP) is one of the two major phenotypes of CRS, with an estimated prevalence of 4.2% in the United States and 4.3% in Europe. While several inflammatory pathways may mediate this condition, an estimated 85% of patients with CRSsNP exhibit Th2 (Type 2) inflammation, characterized by an increase in local eosinophilia, total IgE, interleukin (IL)-4, IL-5, and IL-13. Biologic therapies have proven successful in the treatment of related, Th2-mediated inflammatory conditions, including asthma and atopic dermatitis. As such, there has been significant interest in the role of biologics in the treatment of CRSsNP. Biologics target specific immune cells or inflammatory mediators within the cascade, thus offering treatment efficacy while limiting side effects. There has been a rapid expansion of the literature regarding the role of biologics within the treatment paradigm of patients with medically and surgically recalcitrant CRSsNP. Currently, there are five biologics under investigation or approved for the treatment of CRSsNP by the US Food and Drug Administration. As the study of biologics in the role of CRSsNP management continues to grow at a rapid pace, remaining to date on all aspects of these novel treatment modalities will be critical for the otolaryngologist. Herein, we review the current literature regarding biologic therapy options and offer perspective on the future.

Keywords: Biologics, chronic rhinosinusitis, polyps

INTRODUCTION

Chronic rhinosinusitis (CRS) is a common inflammatory disorder of the paranasal sinuses. The overall prevalence of CRS in Europe by European Position Paper on Sinusitis (EPOS) criteria is 10.9%. Due to the high prevalence of disease, the chronic nature of the condition, and the high quality-of-life impact resulting in lost productivity, the socioeconomic costs associated with CRS are high.3,6 Despite this, there is no cure. Current guidelines dictate that initial management of CRS is medical therapy, followed by endoscopic sinus surgery for medically refractory cases. However, some patients fail to achieve symptomatic control even with both maximal medical and surgical treatment. In these cases, otolaryngologists have limited therapeutic options to offer these patients. Fortunately, as the pathophysiology of this disease process becomes better understood, more targeted treatment options are emerging.

Historically, CRS has been categorized based on phenotype: either CRS with nasal polyps (CRSsNP) or CRS without nasal polyps (CRSsNP). However, new evidence suggests that this is an oversimplification, and that CRS is, in fact, a complex and diverse inflammatory disorder. We now understand that there are multiple endotypes within both CRSsNP and CRSsNP. Three main inflammatory pathways are under investigation: TH1, TH2, and TH17. Each of these inflammatory pathways is characterized by a specific cytokine profile. TH1 (type 1) inflammation is generally associated with CRSsNP, and TH2 (type 2) inflammation is commonly associated with CRSsNP in Caucasian patients. It has also been shown that some patients may have mixed patterns of inflammation.4 Understanding the specific pathophysiology of CRS at an individual patient level by understanding the cytokine profile may allow for targeted, biologic therapies.

The current standard for medical therapy in medically and surgically refractory cases of CRSsNP is corticosteroids, both oral and topical. However, repeated doses of this treatment, particularly oral, is associated with long-term risk.
In these patients, biologics may offer significant benefits. Biologics may decrease inflammation by targeting specific mechanisms within the inflammatory cascade, obviating the need for frequent oral corticosteroids, and offering better control of symptoms while reducing systemic effects and potential complications.8

In recent years, several biologics have been developed for use in systemic inflammatory conditions such as asthma and atopic dermatitis. It was noted that patients with comorbid CRSwNP experienced an incidental improvement in sinonasal symptoms when treated for these other inflammatory conditions, likely due to overlapping pathophysiology. Subsequently, a great deal of interest has been devoted to the role of biologics in the management of CRSwNP, and due to promising early results, a resulting rapid expansion in the volume of research concerning biologics and CRSwNP. Due to this rapid growth, it has been difficult to stay current on the most recent literature. The objective of this review is to provide an update on the most recent literature in the field and to offer perspective on the future role of biologics in the treatment of patients with CRS.

CURRENT BIOLOGICS

There are numerous biologic therapies under investigation or currently used for Th1, Th2, and Th17 mediated inflammatory diseases. These conditions include asthma, atopic dermatitis, inflammatory bowel diseases, idiopathic pulmonary fibrosis, scleroderma, rheumatoid arthritis, and many others. However, as they relate specifically to CRS, there are no biologic therapies under investigation for Th1- or Th17-mediated CRS. There are five different monoclonal antibody therapies specifically targeting Th2-mediated inflammation, which are either under investigation or currently approved by the US Food and Drug Administration (FDA) for CRSwNP.9–14 This is likely due to the overlap between CRSwNP and other Th2-mediated conditions such as asthma and atopic dermatitis, for which these biologics had been initially studied.

To understand the mechanism of action of biologics as adjunct treatments for CRSwNP, it is of utmost importance to understand the pathophysiology of Th2-mediated inflammation. While Th2-mediated inflammation represents a very complex immune cascade, the extent of which is not fully appreciated in vivo, a simplified understanding is as follows: in response to infectious agents, commensal microorganisms, or self-antigens, naïve CD4+ T-cells differentiate into Th2-type T-helper cells as part of adaptive immunity. The Th2 cells then produce various Th2-associated cytokines, including interleukin-4 (IL-4), IL-5, and IL-13. Then, through the action of IL-4 and IL-13, Th2 cells regulate B cell class switching to IgE. IgE then activates innate immune cells (basophils and mast cells), resulting in proinflammatory cell recruitment and further inflammation. Through the action of IL-5, eosinophilia is induced.15 It is at these main points of the Th2 inflammatory cascade that biologic therapies are designed to disrupt (Figure 1).

The first biologic approved in the United States and Europe specifically for the treatment of CRSwNP is dupilumab. Dupilumab is a monoclonal antibody to the alpha subunit of the IL-4 receptor (IL-4Rα). As IL-4 and IL-13 share receptor affinity for the IL-4Rα, this monoclonal antibody inhibits signaling of both cytokines and subsequently, their roles in the pathogenesis of inflammation. Between 2016 and 2017, the LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 were conducted. These were two multinational, multicenter, randomized, double-blind, placebo-controlled, parallel-group studies assessing dupilumab in adults with severe CRSwNP. There were 276 patients enrolled in SINUS-24 and 448 patients enrolled in SINUS-52. Like the other phase 3 clinical trials presented above, dupilumab was found to significantly improve the coprimary endpoints in both studies. At 24 weeks, least squares mean differences in nasal polyp score of the dupilumab treatment group versus placebo group were –2.06 (P < .0001) in SINUS-24 and –1.80 (P < .0001) in SINUS-52. The difference in least squares mean difference in nasal congestion or obstruction score was –0.89 (P < .0001) in SINUS-24 and –0.87 (P < .0001) in SINUS-52. Finally, the difference in Lund-Mackay CT scores was –7.44 (P < .0001) in SINUS-24 and –5.13 (P < .0001) in SINUS-52. Ultimately, the study authors concluded that dupilumab reduced polyp size, sinus opacification, and severity of symptoms and support the use of dupilumab as an adjunct to the standard of care for patients with severe recalcitrant CRSwNP.9 Dupilumab was approved by the FDA for the treatment of CRSwNP in June 2019.

Although dupilumab was the first biologic to obtain FDA approval for the treatment of CRSwNP, omalizumab, an anti-IgE monoclonal antibody, was the first biologic studied for this purpose. Omalizumab was first approved in 2003 for the treatment of allergic asthma.16 However, in a subset of these patients with comorbid CRSwNP, it was noted that sinonasal symptoms subjectively improved and polyp burden objectively improved. From this, an interest in the role of biologics for the treatment of CRSwNP was born. Subsequently, randomized trials were designed to specifically evaluate the efficacy of omalizumab for the treatment of CRSwNP. Between 2017 and 2019, multi-institutional replicate, phase 3, randomized,
double-blind, placebo-controlled studies evaluating the efficacy and safety of omalizumab, labeled the POLYP 1 and POLYP 2 studies, were conducted. There were 5,138 patients with severe CRSwNP enrolled in POLYP 1 and 5,127 enrolled in POLYP 2. At week 24 of the POLYP 1 and POLYP 2 trials, the mean changes from baseline for omalizumab-treated patients compared to placebo controls were as follows: the nasal polyp score was –1.08 versus 0.06 ($P < .0001$) and –0.90 versus –0.31 ($P = .0140$); the nasal congestion score was –0.89 versus –0.35 ($P = .0004$) and –0.70 versus –0.20 ($P = .0017$); and SNOT-22 scores were –24.7 versus –9.6 ($P < .0001$) and –21.6 versus –6.6 ($P < .0001$). Ultimately, Gevaert et al. reported that omalizumab significantly improved endoscopic, clinical, and patient-reported outcomes in severe CRSwNP that did not adequately respond to standard medical therapy. The FDA approved omalizumab for the treatment of CRSwNP on December 1, 2020.

Following these successes, additional monoclonal antibodies, including anti-IL-5 therapies, were specifically studied for the treatment of CRSwNP. These include mepolizumab, reslizumab, and benralizumab. Mepolizumab and reslizumab are both anti-IL-5 antibodies, while benralizumab is an anti-IL-5 receptor antibody. All of these biologics were initially FDA approved for the treatment of eosinophilic asthma. Mepolizumab in 2015, reslizumab in 2016, and benralizumab in 2017. Between 2017 and 2018, mepolizumab was studied in the SYNAPSE trial, a randomized, double-blind, placebo-controlled, parallel-group phase 3 clinical trial. Four hundred and seven patients were included. At week 52, the mean changes from baseline for mepolizumab-treated patients versus placebo controls were as follows: total endoscopic nasal polyp score improved with an adjusted difference in medians –0.73 ($P < .0001$) and a nasal obstruction VAS score with an adjusted difference in means of –3.14 ($P < .0001$). In July 2021, mepolizumab was approved by the FDA for the treatment of CRSwNP. A less studied anti-IL-5 biologic is reslizumab. In a 2006, double-blind, placebo-controlled randomized safety and pharmacokinetic study of 24 subjects with CRSwNP, Gevaert et al. concluded that a single injection of reslizumab reduces the size of nasal polyps for 4 weeks in half of the patients, and nasal IL-5 levels predict the response to anti-IL-5 treatment. Benralizumab was studied in the yet to be published OSTRO phase 3 randomized control trial, in which 413 patients enrolled and available preliminary conclusions suggest primary endpoints were met and nasal polyp size and blockage was reduced.

While there are limitations to each of these trials, there are convincing data to suggest that biologics are effective and do improve disease burden and symptoms for Th2-mediated CRSwNP. However, biologics are not without unique risks and associated costs.

**RISKS OF BIOLOGICS**

As with any treatment modality, biologics are not without risk. It is important for the clinician to weigh the potential risks and benefits and discuss with the patient prior to starting any therapy. Several studies have reported on the adverse events (AEs) of biologics.

Gevaert et al. reported that 14 of 265 patients treated with omalizumab had a treatment related AE. The number of AEs from the placebo group and treatment group was five and nine, respectively. One patient in the placebo group had an AE that led to discontinuation of the study. The most common AEs in the treatment group were headache (8.1%), nasopharyngitis (5.9%), injection site reactions (5.2%), and asthma exacerbation (3.7%).

In the aforementioned study of reslizumab, Gevaert et al. reported that 23 out of 24 patients (95.8%) had at least one AE, with the most common being an upper respiratory tract infection (58.3%). It is important to note that 4 out of 14 (28.6%) subjects who reported upper respiratory infection were in the placebo group. They reported no difference in AEs between treatment groups. However, in a smaller, randomized, double-blind, placebo-controlled trial looking at the efficacy of reslizumab ($n = 14$), Pinto et al. reported no AEs or side effects.

The common AEs reported from mepolizumab are similar to those associated with omalizumab and reslizumab. In descending order, they are headache, nasopharyngitis, oropharyngeal pain, back pain, influenza, arthralgia, and pyrexia. Interestingly, other than oropharyngeal pain, back pain, influenza, and pyrexia, most AEs were higher in the placebo group. In a 2017 study of 105 patients, 10 discontinued treatment due to AEs (six placebo, four treatment group, and one unassigned).

In the aforementioned SINUS-24 and SINUS-52 studies evaluating the efficacy of dupilumab, the most common AEs reported in order from most to least common were nasopharyngitis, nasal polyps, headache, asthma, epistaxis, and injection site erythema. While the incidence of AEs was lower in the treatment group compared to the placebo group SINUS-24, the reverse was true in SINUS-52. In all, seven patients were discontinued from the study due to AEs (five from the placebo group and two from the treatment group). Despite these discontinued patients, no serious AEs were thought to be related to treatment.

**COSTS OF BIOLOGICS**

When considering the role of a new treatment modality, it is critical for the provider to consider the costs of that modality. In a perfect system, decisions would be made irrespective of financial cost, and only weigh the benefits against the risks. However, healthcare delivery is a system with constrained resources, and the cost-effectiveness of a treatment must be considered. In order to determine the cost effectiveness of biologics, which have only been recently used for CRS, researchers have tried to create representative models.

Scangas et al. created a model to compare cost-effectiveness of dupilumab versus endoscopic sinus surgery. The model assumed an annual cost of $31,000 for dupilumab, a single cost of $8,968 for an uncomplicated sinus surgery, and a single cost of $16,877 for a sinus surgery with a major complication. The outcomes of their Markov model comparing the two treatment arms over a 10-year period demonstrated a total cost of $50,436.99 and produced 9.80 quality-adjusted life years (QALYs) in the endoscopic sinus surgery arm, and a total cost of $536,420.22 and produced a total of 8.95 QALYs in the dupilumab arm. In this study, treatment with dupilumab costs 10 times more per QALY than the standard therapy. While there are certainly limitations to this study with assumptions in both groups that may not hold true, this model is one attempt to estimate the cost-effectiveness of biologic treatment.

However, certain groups of patients with CRSwNP are prone to fail standard medical and surgical treatment, such as those with comorbid asthma or aspirin exacerbated respiratory disease. It is postulated that biologics may be relatively more cost-effective in these groups of patients. Yong et al. compared the cost effectiveness of dupilumab to endoscopic sinus surgery and aspirin desensitization in patients with CRSwNP and aspirin exacerbated respiratory disease and found that even in this recalcitrant group, dupilumab was less cost-effective than surgical management with medical therapy.

Overall, our understanding of the cost effectiveness of biologics is limited, with few models of cost-effectiveness available for other frequently used biologics. Additionally, models to date assume biologic use to be long term. However, as the SINUS-52 study shows, once disease control
has been achieved, the interval between treatments may be prolonged with comparable effects, thus reducing the costs of annual biologic therapy. Finally, in future studies, to increase generalizability, there have been calls to include samples from allergy and primary care clinics. Nonetheless, with the evidence available to date, it seems the role of biologics may be reserved for those who have failed traditional medical and surgical therapy for CRSwNP. However, this assumption should be revisited frequently as the costs of a new technology are expected to come down in time, and our knowledge of the effectiveness and effect on QALYs is expected to be refined.

**FUTURE OF BIOLOGICS**

The emergence of biologics has shifted treatment paradigms for CRSwNP. However, given their relative nascency in the treatment of CRSwNP, our understanding of their long-term outcomes is limited. There are currently trials actively recruiting patients designed to study treatment outcomes over longer periods of time, including dupilumab up to 3 years. There are still many questions regarding which patients would benefit most from biologics, and which biologic to prescribe. This is due to heterogeneity in treatment response among patients seen in all of the aforementioned trials. Several studies aim to provide further clarity on this issue. One phase 4 trial currently in the recruitment phase looks to compare dupilumab to omalizumab to placebo at 24-weeks in patients with CRSwNP. There are also ongoing clinical studies in the recruitment phase designed to better understand which patients will be responders to omalizumab and benralizumab.

There is also increasing interest in the investigation of antibodies targeting the IL-33 pathway. IL-33 is expressed by basal epithelial and endothelial cells. It binds to the ST2 receptor and functions by increasing activity of innate lymphocyte cells type-2 and Th2 cells in response to damage or stress. There are currently two biologics that affect this mechanism under investigation: AMG 282 and etokimab. AMG 282 is a monoclonal antibody to the ST2 receptor, preventing its binding to IL-33. A phase 1 trial for AMG 282 has been completed. There are no current phase II trials in progress. Etokimab, previously known as ANB 020, is an anti-IL-33 monoclonal antibody. Recruitment for a phase II clinical trial evaluating the efficacy and safety of etokimab compared to placebo has been completed, and study results are pending. Additionally, investigators are currently evaluating biologics’ role in other pathophysiologies such as allergic fungal rhinosinusitis and CRSsNP.

**CONCLUSION**

Biologics are a promising new treatment option for patients with medically and surgically refractory CRSwNP. Biologics can target specific inflammatory profiles with few serious AEs reported. While questions still exist regarding the optimal use, and further research is needed to clarify the long-term benefits and risks and cost effectiveness of this modality before routine use is recommended, the current knowledge clearly demonstrates benefit to certain patients with CRSwNP.

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