A Primer on Biologic Therapies for Chronic Rhinosinusitis

Michael J. Aw1, Andrea Lasso2, Shaun Kilty3

1University of Ottawa Faculty of Medicine, Ottawa, Canada
2Ottawa Hospital Research Institute, Ottawa, Canada
3Department of Otolaryngology-Head and Neck Surgery, University of Ottawa, The Ottawa Hospital, Ottawa, Canada

Abstract
Chronic rhinosinusitis is a complex multifactorial inflammatory disease that affects up to 12% of the adult population globally. Chronic rhinosinusitis is associated with significant morbidity and represents a large healthcare burden. Despite medical and surgical treatment, a subset of "difficult-to-treat" patients have poor symptom control due to substantial inflammatory disease persistence. These patients represent ideal candidates for biologic therapeutics, which specifically modulate key inflammatory processes implicated in chronic rhinosinusitis pathophysiology. Chronic rhinosinusitis is often dichotomized phenotypically between those presenting with and without nasal polyps. Chronic rhinosinusitis with nasal polyps often represents the more severe disease phenotype and is classically associated with type 2 inflammation mediated by type 2 helper T cells, innate lymphoid cells, immunoglobulin E B cells, basophils, mast cells, and eosinophils. Biologic agents targeting known key mediators of type 2 inflammation have been shown to reduce disease burden. Phase 3 clinical trials studying the effects of anti-immunoglobulin E, anti-interleukin-5/anti-interleukin-5Rα, and anti-interleukin-4/interleukin-13 humanized monoclonal antibodies have shown that these biologics can reduce both polyp size and the need for revision surgeries, improve symptoms, and downregulate inflammatory markers while maintaining an acceptable safety profile. Currently, biologics should be reserved for patients with chronic rhinosinusitis nasal polyps with moderate-to-severe disease who have failed maximal medical and surgical therapy, with sufficient surgery having been previously undertaken. Further studies are needed to better endotype patients to optimize biologic use and compare the relative effectiveness of biologics in difficult-to-treat patients.

Keywords: Chronic rhinosinusitis, monoclonal antibodies, nasal polyps

Chronic rhinosinusitis (CRS) is a complex multifactorial inflammatory disease of the nose and paranasal sinuses that impacts 5% to 12% of the worldwide adult population.1,2 The onset of primary CRS occurs generally between 40 and 60 years of age.1 Chronic rhinosinusitis diagnosis requires both clinical symptoms and mucosal changes observed with either endoscopy or computed tomography (CT).1 This common disease is associated with significant morbidity and has been associated with a substantially reduced health-related quality of life.1 Common symptoms experienced by persons with CRS include facial pain, nasal congestion, loss of olfaction, and headache.1 The quality of life impact of CRS is estimated to be greater than Parkinson’s disease, coronary artery disease (CAD) requiring percutaneous coronary intervention, and moderate chronic obstructive pulmonary disease.4 Moreover, the annual direct cost of CRS treatment ranges from US$5560 to US$5955 per patient with total direct cost attributed to CRS treatment in the United States estimated at upwards of US$60.2 billion.5

The commonly used treatments for CRS focus on the control of inflammation by either regulating mucosal inflammation with topical or systemic corticosteroids, reducing planktonic bacterial burden with antibiotics, and the improvement of sinus ventilation and access for topical therapies, with endoscopic surgeries. However, despite medical and surgical therapy, a subset of patients, often labeled as "difficult-to-treat," do not achieve symptom control. The use of biologic therapies, which target key mediators of the inflammatory process, has been implicated as valuable assets for CRS care, particularly among "difficult-to-treat" patients.1 The significant morbidity and healthcare burden attributed to this disease warrants the study of these inflammatory modulators to better control mucosal inflammation and reduce the burden of disease. Here, we discuss recent advances in monoclonal antibody (mAb) therapies as CRS-specific treatments in the context of the Canadian population.
Chronic Rhinosinusitis Disease Development

Current hypotheses propose that deficiencies in host barrier defenses permit infectious invasion and the resultant skewing of inflammatory responses favoring CRS development. Sinonasal epithelial cell dysfunction is associated with an impairment of barrier function, mucociliary clearance, and the regulation of eosinophils, dendritic cells, T cells, and complement. The sinonasal epithelium is more porous in CRSwNP compared to healthy tissue, which increases its susceptibility to exogenous antigen stimulation. Epithelial disturbance results in the release of epithelium-derived alarmins, IL-33 and thymic stromal lymphopoietin (TSLP), promoting type II inflammatory responses. Ultimately, it is possible that host barrier defects facilitate exogenous antigen exposure, which perpetuates an inappropriate inflammatory response.

Both bacterial and fungal colonization, namely Staphylococcus aureus and Alternaria, have been implicated in CRS disease severity. The intranasal bacterial microbiome of patients with CRS differs from that of healthy controls. It is hypothesized that S. aureus enhances type II inflammation through superantigen effects. Similarly, fungal organisms inhabit nearly 100% of persons with CRS. Alternaria antigen can elicit eosinophil degranulation and fungal wall components, chiefly chitin, and can promote type 2 inflammatory responses. However, antifungal therapies have been largely unsuccessful in treating CRS. Currently, it is believed that microorganisms represent a major disease-modifying factor for a subset of patients but are not directly implicated in CRS development.

Chronic Rhinosinusitis Inflammatory Endotypes

Chronic rhinosinusitis endotypes are generally classified as either type 2 or non-type 2 inflammation. Eosinophilic type 2 CRS is the prevailing disease endotype among North American and European populations. In contrast, individuals with cystic fibrosis and those of Asian descent often present with type 1 and/or type 3 inflammatory profiles. Nonetheless, it is estimated that 80% of nasal polyps from Western populations follow a type 2 profile and 20%-60% of nasal polyposis is attributed to type 2 inflammation in East Asia.

Clinically, type 2 CRS more frequently impacts the ethmoid sinuses and is associated with headaches, nasal polyposis and anosmia, asthma, allergic rhinitis, and aspirin-exacerbated respiratory disease (AERD). In type 2 CRS, exogenous antigen stimulation of nasal epithelium triggers the release of the alarmins IL-25, IL-33, and TSLP. These cytokines enhance IL-4, IL-5, and IL-13 production in type 2 innate lymphoid cells (ILCs), which create a local type 2 inflammatory profile in situ. Additionally, alarmins stimulate and activate myeloid dendritic cells, which migrate to lymphoid tissue and favor the differentiation of naive CD4 T cells into effector type 2 helper T (Th2) cells by presenting antigens in the context of IL-4. Type 2 helper T cells secrete key type 2 cytokines (IL-4, IL-5, IL-13) and encourage isotype class-switching of B cells toward immunoglobulin E (IgE). Immunoglobulin E binding to FceRI receptors on mast cells and basophils, which cross-linked with antigen, induces degranulation and the release of inflammatory markers including histamine, cytokines, pro-angiogenic factors, and proteases. Additionally, IL-5 recruits and activates eosinophils which play a pivotal role in nasal tissue remodeling.

Tissue remodeling in CRS perpetuates the chronicity of the disease and consists of fibrosis, collagen deposition, angiogenesis, osteitis, and mucosal hypertrophy.

Non-type 2 CRS is characterized by neutrophil invasion and represents a mix of type 1 (Th1) and type 3 (Th17) inflammation. Clinically, non-type 2 CRS predominates in the maxillary sinus and has been attributed to pollution and bacterial exposure. Following irritant or pathogen exposure, epithelial cells and macrophages secrete IL-6, IL-8, tumor necrosis factor-alpha, and interferon-gamma (IFN-γ). This promotes Th1 differentiation, resulting in IL-2 and IFN-γ production. Alternatively, IL-6 triggers the differentiation of Th17 cells, which produce IL-17 and incite a neutrophilic response. Of note, in the last 20 years, there has been a significant shift in some Asian countries toward a greater prevalence of eosinophilic CRS, which further highlights the importance of type 2 CRS endotype.

Difficult-to-Treat Patients

While a majority of patients achieve adequate disease control with conventional medical options including nasal irrigation, intranasal corticosteroids, systemic corticosteroids, and antibiotic therapies with or without endoscopic sinus surgery (ESS), a subset of patients have recalcitrant disease. This difficult-to-treat population require frequent revision surgeries and repetitive courses of systemic corticosteroids and antibiotic therapies (among others), which have appreciable adverse effects. Specifically, 15%-20% of patients require revisional ESS within 5 years of their first surgery. Notably, uncontrolled type 2 inflammation is associated with this “difficult-to-treat” cohort. Patients with comorbid asthma and/or AERD generally have more severe CRSwNP and are more...
likely to have recurrent CRSwNP. Likewise, elevated blood and mucosal eosinophilia are strongly associated with severe disease and 5-year CRSwNP recurrence compared to those with non-eosinophilic CRSwNP. Essentially, type 2 CRS represents the predominant endotype associated with “difficult-to-treat” patients and therapeutic targeting of this subtype is the focus of this review.

**BIOLOGIC THERAPIES**

**Anti-Immunoglobulin E Antibodies**

Omalizumab, an anti-IgE humanized mAb, is currently indicated in patients with moderate-to-severe allergic asthma who are not well controlled with inhaled corticosteroids and inhaled long-acting β2 agonist bronchodilators. In addition to its proven efficacy in treating other atopic diseases, there is compelling evidence that omalizumab may represent an effective treatment for eosinophilic CRSwNP. A randomized double-blinded clinical trial of 24 participants in Belgium found that biweekly subcutaneous (SC) omalizumab significantly reduced total nasal endoscopic polyp scores (TPS) in 8 weeks (P = .001). Similarly, the Lund–MacKay CT score, a radiologic measure of paranasal sinus inflammation, significantly improved in the intervention cohort compared to placebo after 16 weeks. These positive findings have been substantiated by 2 recent phase 3 multicenter clinical trials, POLYP1 and POLYP2. Collectively, 265 patients were randomized 1:1 to receive 600 mg SC omalizumab every 2 and 4 weeks and intranasal mometasone or intranasal mometasone alone for 24 weeks. Sino-Nasal Outcome Test 22 (SNOT-22) scores improved between the 2 cohorts as early as 4 weeks and were clinically different in both POLYP1 and POLYP2 at the 24-week endpoint for the treatment versus the placebo cohorts (−16.12 (95% CI = −21.86 to −10.38), P < .0001 and −15.04 (95% CI = −21.26 to −8.82), P < .0001, respectively). The mean TPS treatment arm differences between the omalizumab and placebo groups were −1.14 (95% CI = −1.59 to −0.69; P < .0001) and −0.59 (95% CI = −1.05 to −0.12; P = .0140) in POLYP1 and POLYP2, respectively. At 24 weeks, the University of Pennsylvania Smell Identification Test (UPSIT) scores improved significantly compared to baseline and placebo in the omalizumab treatment arms. Similar findings were reported for nasal congestion scores, loss of smell scores, and postnasal drip scores. Interestingly, TPS improvements associated with omalizumab treatment were comparable among patients with comorbid asthma and AERD to those without either comorbidity. Additionally, patients with comorbid asthma in the treatment arm saw significant improvements in Asthma Quality of Life Questionnaire scores. Conversely, a small randomized American clinical trial found SC omalizumab every 4 weeks (0.016 mg/kg/UL total serum IgE/mL) to be an ineffective treatment for polyp reduction and symptom control while studying 14 patients with CRSwNPs and comorbid asthma and elevated blood IgE levels (30-70 IU/mL). Unlike the POLYP studies, which had positive findings with omalizumab treatment, patients selected in this study did not necessarily present with blood eosinophilia (>300 cells/μL) which may explain discrepancies in treatment efficacy. Omalizumab appears to be well tolerated, with few adverse events reported, the most common being headache, injection site reaction, and nasopharyngitis. Overall, these results support the use of omalizumab for CRSwNP with or without comorbid asthma. Currently, in Canada, omalizumab has been approved for the treatment of severe CRSwNP refractory to intranasal corticosteroids.

**Anti-Interleukin-4/Interleukin-13 Antibodies**

Interleukin-4 receptor alpha (IL-4Rα) represents a promising target for the treatment of CRSwNP. The blockade of IL-4Rα targets 2 critical type 2 inflammatory cytokines as IL-4 and IL-13 both signal via this receptor to elicit their effects. Likewise, both cytokines are directly involved in the tissue remodeling of CRSwNP. Dupilumab is a humanized mAb that binds to the alpha subunit of the IL-4Rα. It has been shown to be effective in the treatment of eosinophilic asthma. Currently, dupilumab treatment for CRSwNP has been studied in a single phase 2a study and phase 3 clinical trials. Two multicenter, international phase 3 trials, SINUS24 and SINUS52, have elucidated the therapeutic benefit of dupilumab for CRSwNP. In SINUS24, 276 participants were randomized 1:1 to receive biweekly 300 mg SC dupilumab plus nasal steroids or steroids alone for 24 weeks. In SINUS52, 448 participants were randomized 1:1:1 to receive 300 mg SC dupilumab biweekly plus nasal steroids for 52 weeks, 300 mg SC dupilumab biweekly for 24 weeks followed by 28 weeks of 300 mg SC dupilumab every 4 weeks or placebo. Both studies demonstrated strong nasal polyp score (NPS) improvement compared to placebo at 24 weeks (the least squares mean change (LSMD) = −2.06 (95% CI, −2.43 to −1.69), P < .0001) and (LSMD = −1.80 (95% CI = −2.10 to −1.51), P < .0001) for SINUS24 and SINUS52, respectively. At 52 weeks, the collective dupilumab groups continued to demonstrate improved NPS compared to placebo (LSMD = −2.40 (95% CI, −2.77 to −2.02), P < .0001). Similarly, SNOT-22 scores were significantly improved compared to placebo at both 24 weeks for SINUS24 (LSMD = −21.12 (95% CI = −25.17 to −17.06) P < .0001) and SINUS52 (−17.36 (95% CI = −20.87 to −13.85), P < .0001), respectively. Moreover, both studies demonstrated that the dupilumab treatment arms have significantly improved Lund–MacKay CT scores, UPSIT scores, and total symptom scores at 24 weeks and 52 weeks. Dupilumab treatment was associated with 24-week reductions in key inflammatory biomarkers including total serum IgE, eotaxin-3, eosinophil cationic protein, and nasal IL-5 levels in SINUS24 and SINUS52. However, discontinuation of dupilumab was associated with the return of baseline blood eosinophils. Sub-group analyses demonstrated that the effects of dupilumab on CRS symptom control were comparable for those with comorbid AERD and/or asthma. Dupilumab treatment improved asthma symptoms and lung function independent of blood eosinophil levels. Dupilumab appears to be well tolerated with the most frequent issues including nasopharyngitis, epistaxis, headache, and injection site reactions being more common in the placebo arms; however, vigilance with new medications is always warranted. Given the high-quality evidence, dupilumab represents a viable option for difficult-to-treat CRSwNP and has been recently approved for CRSwNP treatment in Canada as an add-on maintenance treatment for disease inadequately controlled with systemic steroids and/or surgery.

**Anti-Interleukin-5 Antibodies**

Interleukin-5 is considered the most important cytokine in the recruitment and activation of eosinophils. Eosinophilia is a hallmark cellular infiltrate in CRSwNP and plays a significant role in disease propagation and tissue remodeling associated with polyp formation. Several humanized anti-IL-5 antibodies, namely, reslizumab, mepolizumab, and benralizumab, have been studied in CRSwNP (see Figure 1). A randomized, 2-center study determined that a single 1 mg/kg or 3 mg/kg SC dose of reslizumab was able to significantly reduce blood eosinophilia for up to 8 weeks among patients with CRSwNP. However, there was rebound eosinophilia noted 24 weeks post-injection. Moreover, while there was evidence of TPS improvement in the treatment arm, there was unconvincing clinical improvement in other symptoms. Alternatively, mepolizumab, another anti-IL-5 mAb, has demonstrated more promising results. A randomized controlled study of 105 patients with bilateral recurrent CRSwNP requiring surgery found that 750 mg mepolizumab every 4 weeks (6 doses total) significantly reduced the need for ESS and reduced adverse events reported, the most common being headache, injection site reaction, and nasopharyngitis. Overall, these results support the use of omalizumab for CRSwNP with or without comorbid asthma. Currently, in Canada, omalizumab has been approved for the treatment of severe CRSwNP refractory to intranasal corticosteroids.
nasal polyposis severity visual analog scores (VAS) (treatment difference at week 25 favoring mepolizumab \(=1.8, 95\% \text{ CI} -2.9 \to -0.8; P = .001)\). While the SNOT-22 scores improved for all study arms, there was a clinically and statistically significant difference from baseline in the SNOT-22 scores at 25 weeks favoring the mepolizumab group (\(=13.2, 95\% \text{ CI} -22.2 \to -4.2, P = .005\)). At the study endpoint of 25 weeks, the mepolizumab group demonstrated significant improvements in olfactory loss VAS (\(P < .001\), rhinorrea (\(P < .001\)), and peak nasal inspiratory flow (\(P = .027\)), compared to placebo. More recently, SYNAPSE, a phase 3 multicenter clinical trial compared 1:1 100 mg mepolizumab SC every 4 weeks for 52 weeks (n = 207) against placebo with standard of care (n = 201) in patients with refractory CRSwNP. The treatment arm successfully achieved greater primary endpoint outcomes at 52 weeks including greater relative reductions in TPS (adjusted difference in medians \(=0.73, 95\% \text{ CI} -1.11 \to -0.34; P < .0001\)) and nasal obstruction VAS scores during weeks 49-52 from baseline (\(=3.14, 95\% \text{ CI} -4.09 \to -2.18; P < .0001\)) compared to placebo. Likewise, mepolizumab treatment was associated with significant reductions in SNOT-22 scores (\(P = .003\), olfactory loss VAS scores (\(P = .02\)), and patients requiring systemic corticosteroids (\(P = .02\)) at study endpoint. Collectively, anti-IL-5 biologics appear well tolerated. The most common adverse events include upper respiratory tract infections, headache, epistaxis, pyrexia, oropharyngeal pain, and injection site reactions. Mepolizumab is currently approved as an add-on maintenance treatment in patients with CRSwNP inadequately controlled with intranasal corticosteroids.

More recently, benralizumab, an anti-IL-5Ra mAb, may have greater anti-eosinophilic effects by directly targeting IL-5Ra-expressing cells independent of ligand. Further, the antibody is afucosylated, which induces cell-mediated cytotoxicity of eosinophils. A phase 3 randomized clinical trial, OSTRO, randomized 1:1, 413 patients with refractory CRSwNP to receive benralizumab 30 mg SC every 8 weeks or placebo for 40 weeks. Benralizumab treatment was associated with significant improvements in the study’s primary endpoints, TPS (between-group difference, \(-0.57, 95\% \text{ CI} -0.85 \to -0.29; P < .001\)) and biweekly average nasal blockage scores (\(-0.27, 95\% \text{ CI} -0.46 \to -0.08, P = .005\)) compared to placebo. However, benralizumab treatment failed to significantly clinically change SNOT-22 scores or the need for surgery compared to control. Benralizumab has demonstrated notable therapeutic benefits for severe asthma and there is evidence to suggest that patients with comorbid asthma and CRSwNP are more likely to respond to benralizumab after mepolizumab treatment compared to those with asthma alone. A small study of 10 patients with eosinophilic CRSwNP and severe asthma receiving 30 mg SC benralizumab every 4 weeks found all clinical parameters improved at 24 weeks. Specifically, the following markers of disease severity decreased including TPS (\(P < .001\)), SNOT-22 scores (\(P < .001\)), Lund–Mackay CT scores (\(P < .001\)), and blood eosinophila (807.3 ± 271.1 cells/μL to 0 cells/μL, \(P < .0001\)). Despite the results from the OSTRO study, the US Food and Drug Administration did not approve the use of benralizumab as a treatment for inadequately controlled CRSwNP and requested additional clinical data from the manufacturer. A second phase
3 clinical trial evaluating the safety and efficacy of benralizumab in eosinophilic CRSwNP is currently ongoing.38

Future Therapeutic Targets
Prevaling evidence implicates alarmins, IL-25, IL-33, and TSLP as key regulators of type 2 inflammation (Figure 1). These mediators, expressed by epithelial lymphoid cells and ILCs, favor activation and recruitment of type 2 ILCs, eosinophils, and Th2 cells.39

Animal studies have shown anti-IL-33 treatment reduces mucus thickness, subepithelial collagen deposition, and neutrophil infiltration within the nares.16 Currently, the ECLIPSE phase 2 clinical trial of SC etokimab (anti-IL-33 mAb) treatment every 4 or 8 weeks is being conducted with 106 patients with CRSwNP. Unfortunately, a press report by AnaptysBio, Inc. explained that etokimab treatment failed to achieve statistically significant improvements in NPS or SNOT-22 scores at the 8-week endpoint.50 They plan on re-assessing their data at the 16-week study endpoint. Interestingly, a murine study reported that anti-IL-33 treatment reduced neutrophilic infiltration but failed to mitigate eosinophilic infiltration.56 This may limit etokimab’s use for eosinophilic disease, but this biologic may have a niche role in the treatment of neutrophilic CRS.

TLSP levels are greater in the nares of patients with CRSwNP and promote IL-5 production by macrophages in nasal polyp tissue.41 Tezepelumab (anti-TLSP mAb) treatment has been studied in a phase 2b clinical trial of patients with severe asthma with or without nasal polyps. A total of 550 patients were randomized 1:1:1:1 to receive SC tezepelumab 70 mg every 4 weeks, 210 mg every 4 weeks, 280 mg every 2 weeks, or placebo. Irrespective of prior nasal polyp status, at the 52-week endpoint, the tezepelumab-treated cohorts had significant reductions in annualized asthma exacerbation rates, reductions in blood eosinophils, FeNO, IL-5, and IL-13 levels compared to controls.42 Currently, a multicentered phase 3 trial is underway to evaluate the efficacy of tezepelumab for CRSwNP.43

While many biologics are currently available, no trial to date has systematically compared the relative effectiveness of 1 biologic against another. A case report of a patient with severe asthma, AERD, and CRSwNP reports benralizumab treatment reduced blood eosinophil levels but failed to improve CRSwNP symptoms; however, subsequent dupilumab treatment clinically improved CRSwNP symptoms in the patient.44 Unfortunately, this represents low-level evidence and cannot be generalized to other patients. As a relatively novel therapeutic avenue, it is important to assess the relative effectiveness of the varying biologics.

A 2021 systematic review and network meta-analysis compared 29 randomized control trials from the available biologics for CRSwNP and evaluated the relative benefit of these therapeutics with regards to health-related quality of life, sinusitis symptoms, smell, rescue oral corticosteroids, rescue surgery, nasal polyp size, radiologic severity, and adverse events.45 The analyses revealed that collectively omalizumab, dupilumab, mepolizumab, and benralizumab show health-related quality of life improvements compared to placebo. However, when the biologics were directly compared, dupilumab data were suggestive of superiority in all 7 measured domains.46 However, this review was limited by the small sample sizes, and heterogeneous study cohorts and design. As relatively novel therapeutic agents, the study of long-term outcomes, further patient stratification within pathophysiological endotypes, and considering external factors such as patient values and cost are necessary to optimize biologic choice.

Biologic Therapy Guidelines
In a publicly funded healthcare system, the cost-effectiveness of biologics heavily influences the guidelines for their use in CRSwNP.46 Unfortunately, with few exceptions, in Canada, there is currently no publicly funded coverage of biologic therapy for CRSwNP and patients must rely on private insurance, pay out of pocket, or rely on the beneficence of pharmaceutical companies. Chronic rhinosinusitis biologics represent significant costly therapeutics with current annual individual costs varying from CAD$31,000 to CAD$40,000, in contrast to the estimated annual cost of ESS of CAD$3510.31 in 2014.47,48 Scangas et al49 implemented a Markov decision-tree economic model to estimate the long-term cost of ESS versus dupilumab as a function of quality-adjusted life years. They conclude dupilumab is less effective and more costly than surgery including revision procedures.50 While the short-term cost of biologic therapy is substantially greater than that of alternative treatments, it is difficult to truly estimate the long-term value of biologic use. A retrospective evaluation of the treatment cost for patients with asthma and CRSwNP based on insurance claims showed higher costs for prescriptions other than omalizumab in those taking omalizumab compared to those who did not take the biologic. Surgery rates were also higher for omalizumab users. These results are limited to patients with asthma and CRSwNP and are subject to bias due to the severity of the disease of the population studied. A pre-post analysis found that the need for surgery decreased after 6 months of use of omalizumab from about 3 to 2 surgeries in 10 years.50 Prospective studies evaluating the cost-effectiveness of mAbs for the CRSwNP indication are needed. Further, patients with olfactory loss have an underappreciated handicap, which in some instances prevents gainful employment in their current occupation while anosmia also represents a safety issue for the patient as well as any of their dependents. Further studies are required to appreciate the long-term implications and impact of biologic management. Practically, the consumer cost of biologics will likely have to reduce significantly before biologics can be more broadly integrated into a publicly funded CRS treatment model. A recent Canadian rhinology consensus statement provides an evidence-based framework with 11 considerations to help guide decisions to use biologic treatment for CRSwNP46 From this framework, at this time biologics should only be considered for patients with CRSwNP with moderate-to-severe disease who have failed maximal medical and surgical therapy, with sufficient surgery having been previously undertaken. Comorbid type 2 diseases are not required to consider biologic therapy in the setting of CRSwNP but may favor better systemic treatment outcomes. Physicians should evaluate patient responses regularly and annually with a determination made at 16 weeks after treatment onset to determine treatment continuation, using both objective and subjective measures of disease improvement.46

CONCLUSION
Chronic rhinosinusitis represents a prevalent chronic disease in the adult population and it represents a significant burden on health and healthcare resources. “Difficult-to-treat” patients with recurrent CRSwNP despite conventional medical and surgical treatment represent a population requiring further therapeutic intervention. Biologic therapies, which target critical signaling cascades within type 2 inflammation, are promising supplementary treatment options. For CRSwNP treatment, these disease-modifying agents have been shown to improve objective and subjective clinical signs and symptoms of the disease while reducing inflammatory biomarkers. However, biologic therapy treatment effects are largely transient, and relapse occurs following the termination of biologic treatment. Active studies are underway to evaluate the effectiveness of biologic...
therapies targeting alarmin cytokines, namely IL-33 and TSLP. Healthcare resource stewardship should be considered when selecting biologic therapies because of their significant financial burden. Current guidelines recommend that biologics be reserved for patients with moderate-to-severe disease who have failed maximal medical therapy and adequate sinus surgery. Further evidence is needed to evaluate the long-term effects of biologic therapy and the impact of combined therapies. Disease confounding prior to initiating therapy may prove beneficial to maximize the benefit seen from biologic therapies.

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