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The Role of Biologics in Chronic Rhinosinusitis With Nasal Polyps

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Abstract

Biologic therapy is a new treatment option for patients with chronic rhinosinusitis with nasal polyps (CRSwNP). Currently, the only biologic with Food and Drug Administration–approval status for CRSwNP is dupilumab. Several other biologics are likely to be approved for CRSwNP, including mepolizumab and omalizumab, based on their promising phase 3 trial results. The role of biologics in the treatment paradigm requires consideration of multiple factors that have yet to be clearly established. This includes identifying patients most appropriate for biologic therapy while considering long-term safety and cost-effectiveness in the context of patient preferences and goals.

Keywords

biologics; dupilumab; mepolizumab; omalizumab; benralizumab; chronic rhinosinusitis with nasal polyps (CRSwNP); nasal polyps

Chronic rhinosinusitis (CRS) is a symptomatic chronic inflammatory syndrome of the nose and paranasal sinuses that affects 6% to 12% of patients in the Western world.[1-4] Chronic rhinosinusitis with nasal polyps (CRSwNP) accounts for approximately 20% of all CRS in the United States.[5,6] It is associated with increased morbidity and an annual health care cost burden of US$5.7 billion.[7-9] An estimated 85% of patients with CRSwNP exhibit type 2 (T2) cytokine profiles with increased local eosinophils and total IgE.[10-12] As such, the advent of biologics, which target and reduce T2 inflammation, are novel treatment options for patients with recalcitrant CRSwNP.[13] The role of biologics in the treatment paradigm requires thoughtful consideration of multiple factors, including disease severity, risk of polyp recurrence with medical or surgical treatment, patient preferences and goals, safety, and cost-effectiveness.

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Declaration of Conflicting Interests

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The rapid expansion in research assessing the efficacy of biologics in refractory CRSwNP has led to promising therapeutic options. Monoclonal antibody targets against IL-4Rα, IgE, and IL5/Rα in CRSwNP have been completed or are currently in phase 3 clinical trials. Dupilumab (Dupixent; Sanofi and Regeneron) is currently the only Food and Drug Administration (FDA)-approved biologic agent in the United States and Europe for the treatment of CRSwNP. Dupilumab is an anti-IL4Rα antagonist that prevents the binding of IL-4 and IL-13 to its receptors and blocks downstream signaling of the T2 inflammatory pathway. Two international, double-blind, placebo-controlled phase 3 studies, LIBERTY NP SINUS-24, and LIBERTY NP SINUS-52, included 724 patients with refractory CRSwNP and assessed efficacy of dupilumab 300 mg subcutaneous injection every 2 weeks or 4 weeks for 24 or 52 weeks.[14] All patients were also treated with mometasone furoate nasal spray during the study. Almost two-thirds (63%) of subjects had ≥1 nasal polyp surgery, with the most recent surgery being a mean ± SD 7 (6.4) years prior to participating in the trial. Both studies observed significant improvement in co-primary end points of least mean difference in nasal polyp score compared to placebo (−2.06; 95% CI: −2.43 to −1.69 in LIBERTY-24; −1.80; 95% CI: −2.10 to −1.51 in LIBERTY-52) and nasal congestion score (−0.89; 95% CI: −1.07 to −0.71 in LIBERTY-24; −0.87; 95% CI: −1.03 to −0.71 in LIBERTY-52). Dupilumab improved symptoms, including sense of smell and disease-specific quality of life. Pooled analyses observed decreased systemic corticosteroids or nasal polyp surgery in the dupilumab group by 76% during the treatment period.

Omalizumab (Xolair) has completed 2 phase 3 trials, POLYP I (n = 138) and POLYP II (n = 127), with promising results.[15] Subjects were randomized to subcutaneous omalizumab versus placebo for 24 weeks. Omalizumab dosing was based on weight and serum IgE levels. Both trials showed a significant mean improvement in co-primary end points. Compared to placebo for nasal polyp score, the treatment arm difference was −1.14 (95% CI: −1.59 to −0.69) in POLYP I and −0.59 (95% CI: −1.05 to −0.12) in POLYP II. For the nasal congestion score, the treatment arm difference was −0.55 (95% CI: −0.84 to −0.25) in POLYP I and −0.50 (95% CI: −0.80 to −0.19) in POLYP II. The total nasal symptom score (includes nasal congestion, sense of smell, runny nose, and postnasal drip), individual symptoms such as sense of smell, and disease-specific quality of life significantly improved from baseline in the omalizumab group compared to placebo. Ongoing is an open-label extension study of participants who completed phase 3 studies (NCT03478930).

Mepolizumab (Nucala; GlaxoSmithKline) has completed a phase 3 trial (SYNAPSE; NCT03085797), which included 413 subjects with CRSwNP. Subjects were randomized to mepolizumab 100-mg subcutaneous injection versus placebo every 4 weeks for 52 weeks while receiving background therapy of mometasone furoate nasal spray. Early results show treatment with mepolizumab had a significant difference in median nasal polyp score compared to baseline (−0.73; 95% CI: −1.11 to −0.34) and nasal obstruction visual analog score compared to baseline (−3.14; 95% CI: −4.09 to −2.18; unpublished data).[16]

Benralizumab (Fasenra; AstraZeneca), a monoclonal anti-IL5Rα antibody, is being studied in CRSwNP in 2 phase 3 trials, OSTRO (NCT03401229) and ORCHID (NCT04157335). Both trials are currently ongoing at this time.

These current studies on biologic agents in CRSwNP are encouraging, especially with having 1 already FDA-approved. Biologics appear to be favorable options in patients with severe polyp disease who have failed medical management and/or surgical intervention. The initial management of CRSwNP is the use of local corticosteroids given its efficacy in suppressing T2 inflammation.[3,17] Depending on the severity of the disease, topical corticosteroids can reduce nasal polyp size, improve symptoms, and reduce polyp recurrence after surgery once the polyp burden is removed.[18,19] The effect size is greater in CRSwNP compared to CRS without NP, and long-term use of topical corticosteroids is effective and safe.[3] However, a considerable shortcoming of topical corticosteroids is inconsistent and inadequate delivery to sinuses, which is more challenging when there is a substantial polyp burden.[20] Improved delivery methods including off-label large-volume corticosteroid nasal irrigations and the breath-assisted device can improve distribution and penetration.[18,21-24] Systemic corticosteroids are often effective in addition to topical corticosteroids for uncontrolled or partially controlled symptoms, but benefits do not last once discontinued, and there are significant adverse effects.[25-29]

Patients with severe or refractory disease may be good candidates for biologic therapy. Based on the risk-benefit evaluation, the adverse effects of long-term systemic corticosteroid use outweigh advantages, so should only be considered for short-term use.[28,29] Based on the updated 2020 European Position Paper on Rhinosinusitis and Chronic rhinosinusitis, ≥2 corticosteroid courses per year or long-term use (>3 months) is considered a criterion (multiple need to be met) for considering a biologic for CRSwNP.[3,30] Thus, patients requiring repeat systemic corticosteroids may be a subset of recalcitrant polyps that deserve consideration of a biologic agent.

Patients with severe disease who fail maximal medical therapy alone are recommended to do functional endoscopic sinus surgery. Up to 50% of patients with CRSwNP have a history of sinonasal surgery.[31] The rate of polyp recurrence is not insignificant, with studies showing a recurrence rate between 40% and 60%.[32,33] The recurrence is likely because underlying causes of the inflammation driving polyp formation are not adequately addressed during surgical intervention. Thus, patients who have recurrence despite surgery may benefit from a biologic agent. Additionally, patients who want to avoid surgery or are not eligible for surgery should be considered for a biologic agent.

As part of determining which patients would benefit from a biologic agent, it is important to understand the risk factors associated with recurrent disease. In a meta-analysis that included 45 studies of patients with CRSwNP who underwent sinus surgery, the overall rate of revision surgery was approximately 19%.[34] Risk factors associated with revision surgery included prior polypectomy, aspirin-exacerbated respiratory disease (AERD), allergic fungal rhinosinusitis, and asthma, so these patients are likely good candidates for biologic therapy. Wang and colleagues observed that subjects with combined CRSwNP and asthma endotype have more severe T2 inflammatory patterns compared to CRSwNP-alone endotype based on findings from whole-transcriptome RNA sequencing.[35] Based on this evidence, systemic biologic therapy in patients with both upper and lower airway disease may be a reasonable consideration as it can improve both conditions due to shared pathogenic pathways.

Biologics generally have a favorable safety profile based on already conducted clinical trials. In the phase 3 studies assessing dupilumab for nasal polyp disease, a small number of subjects receiving dupilumab had treatment-emergent adverse events including conjunctivitis or eosinophilia.[14] Long-term follow-up and post-marketing analyses will be essential to determine the frequency of these events and determine other unforeseen events associated with these medications. As observed in the LIBERTY-24 trial, discontinuation of drug results in worsening symptoms.[14] This emphasizes that biologic agents are not disease-modifying drugs or curative, and continued use is likely needed. Also unknown at this time is the long-term efficacy of these drugs in CRSwNP in maintaining benefit.

The cost-effectiveness of biologics compared to standard of care, including ESS, needs to be considered. In a systematic review, the US's overall cost for ESS ranged between US$8200 and US$10,500 in 2014.[36] Biologic wholesale acquisition cost varies between US$30K to US$40K depending on the specific biologic.[37] In a cost-effectiveness analysis performed of all biologic therapies for asthma, the estimates did not meet benchmark effectiveness thresholds.[38] Furthermore, the 2018 report stated that costs of biologics would need to be reduced between 62% and 80% from the wholesale acquisition cost to meet cost-effectiveness thresholds. A cost-utility analysis using a Markov model showed that ESS strategy, including primary and revision surgery, was more cost-effective than dupilumab for CRSwNP.[39] More studies are needed to determine whether long-term or routine use of biologic therapy is truly a sustainable treatment based on evidence that biologics is a costly intervention.

Multiple questions remain unanswered. The role of biologics in relation to the timing of surgical interventions and combination approaches needs to be investigated. Determining tissue endotype and developing biomarkers are important for patient selection and determining response to biologic therapy. Recommendations by a National Institutes of Health–sponsored workshop and the European Forum for Research and Education in Allergy and Airway Disease (EUFOREA) have provided recommendations on incorporating biologic therapy into care pathways.[30,40] The EUFOREA recommendations provide guidance on patient selection for biologics based on the history of sinonasal surgery already performed or not. If a patient has had no history of surgery, then the patient should meet 4 of the following criteria (or 3 criteria if there is a history of surgery): (1) evidence of T2 inflammation, (2) 2 or more courses of corticosteroids in the past 1 year, (3) significantly impaired quality of life, (4) significant loss of smell, and (5) diagnosis of comorbid asthma. Although based on expert opinion, these guidelines are helpful for physicians when deciding if biologic treatment is appropriate for their patients. Ultimately, physicians should engage in shared decision-making conversations with their patients with a focus on patient preferences and goals. These criteria can be helpful in discussing the utility of biologics for individual patients.

In summary, the role of emerging biologics in the treatment algorithm of CRSwNP is still being developed. Based on available data, biologic agents may be beneficial in patients with persistent polyps despite maximal medical therapy, have recurrence despite surgery, or have T2 comorbid allergic diseases including moderate to severe asthma or AERD. Future studies and real-world evidence will determine how biologics fare in the long run. As new evidence

develops regarding biologics for CRSwNP, it will continue to inform patient selection and practice management.

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