

Editorial

Biologics for chronic rhinosinusitis with nasal polyps (CRSwNP)

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Nasal polyps, like asthma, have multiple phenotypes but are rarely malignant. Until recent decades, they were the preserve of the ear, nose, and throat surgeon, with operative removal being the main therapeutic option. Advances such as the sinus computed tomography scan, the nasendoscope, and endoscopic sinus surgery with resulting tissue examination have prompted research that has altered their management, particularly that of chronic rhinosinusitis with nasal polyposis (CRSwNP). CRSwNP is a heterogeneous inflammatory condition with bilateral nasal polyps in the mucosa of the nose and paranasal sinuses, predominantly mediated by type 2 inflammation and often associated with comorbid asthma and/or aspirin-exacerbated respiratory disease (AERD).^{1,2} As a result of symptoms of nasal obstruction and discharge, reduction in smell, taste, and sleep quality, CRSwNP has significant deleterious effects on quality of life and ability to function.²

Pharmacotherapy is now the first-line treatment,¹ with surgery reserved for individuals failing to respond. Nasal saline irrigation, topical corticosteroids, antileukotrienes, antibiotics, topical antihistamines, and topical diuretics have shown some therapeutic efficacy, whereas use of oral corticosteroids can both reduce polyp size and restore olfaction temporarily. None of these options is curative, and for many patients, despite continued therapy, symptomatic polyp recurrence will occur at some stage. Difficult-to-treat patients have a more severe disease requiring high systemic corticosteroid use and/or multiple sinonasal operations. These include, but are not limited to, phenotypes of CRSwNP such as AERD, allergic fungal rhinosinusitis, and eosinophilic granulomatosis with polyangiitis. CRSwNP can be associated with asthma, often severe, with similar underlying eosinophilic pathology,^{1,2} including type 2 innate lymphocytes.³

A more recent advance—the development of mAb drugs—is set to have a major impact on the treatment of CRSwNP, as it has already begun to do for asthma. These biologic inhibitors of key effectors of type 2 inflammation provide add-on therapy for patients with severe, uncontrolled CRSwNP, resulting in

significant improvements in a proportion of patients, albeit at considerable financial cost.⁴ Understanding the endotype of responders and using this to predict responsive phenotypes is increasingly important. The predominance of eosinophilia and IL-5 in Western polyps suggested that monoclonals directed against the latter would prove therapeutic. This is the case for mepolizumab, which has been approved for CRSwNP by the US Food and Drug Administration. Monoclonals directed against IgE (omalizumab) and the IL-4 receptor α -subunit (IL-4R α), which is common to both IL-4 and IL-13 receptors (dupilumab), also reduce nasal polyp size and symptoms, with studies of others directed against thymic stromal lymphopoietin awaited.⁴

In the current issue of the *Journal of Allergy and Clinical Immunology*, Gevaert et al⁵ report on an open-label extension evaluating the efficacy, safety, and durability of responses to omalizumab in adults with CRSwNP who had completed the double-blinded POLYP 1 and POLYP 2 trials.⁶

Of the 265 participants from the original study, 249 either continued taking omalizumab or switched to omalizumab from placebo for 28 weeks, alongside ongoing use of nasal mometasone furoate. They were followed for a further 24 weeks after omalizumab discontinuation. The patients selected for these studies were moderately affected, with a nasal polyp score (NPS) of 5 or higher, moderate or severe nasal congestion, and 22-Item Sino-Nasal Outcome Test (SNOT-22) scores of 20 or higher; 59% of participants had undergone 1 or more sinus operations. Omalizumab had significantly reduced polyp and nasal congestion scores in blinded use.⁶ The open-label extension with omalizumab showed a further modest decrease in polyp and congestion scores from week 24 to week 52, suggesting that the full benefit of treatment is not reached until after 6 months. Discontinuation of omalizumab was associated with gradual increases in polyp and congestion scores, although not to pretrial levels, by week 72. Extrapolation of the data suggests a prolonged rather than a permanent disease-modifying effect.

The estimated reduced need for surgery (defined by an NPS of 4 or lower and improvement of 8.9 points or more in SNOT-22 score) was found in a quarter of those treated with omalizumab. Quality of life showed a 28.47-point improvement in SNOT-22 score (>3 times the minimally clinically important difference) after 52 weeks of omalizumab therapy. Although loss of smell improved, it remained within the anosmic range.

Asthma, mostly mild to moderate, was present in 57.0% of patients. The improvement in Asthma Quality of Life Questionnaire score at week 52 just exceeded the minimally clinically important difference (0.5 points) in patients who switched to omalizumab from placebo (0.52 points) and was higher (0.95 points) in those who continued taking omalizumab, suggesting that asthma outcomes also improved with longer treatment. Patients with comorbid asthma and AERD, compared with patients with neither, had similar mean improvements in polyp and congestion scores at week 52.⁵

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TABLE I. Suggested considerations for using biologics in CRSwNP

When to begin a biologic	When to continue a biologic
Major considerations: - Evidence of type 2 inflammatory polyps (≥ 1 of: eosinophils on polyp histology; peripheral blood eosinophilia $\geq 0.3 \times 10^9/L$; clear [systemic] steroid-responsiveness) - Significant impairment of quality of life (SNOT-22 score ≥ 40 points) despite good concordance with intranasal corticosteroids (unless contraindicated) and previous surgery (if patient is a viable candidate) and use of systemic corticosteroids for nasal disease in the past 12 mo (unless contraindicated) Additional considerations: - Impact of loss of smell (eg, on profession) - Sleep-disordered breathing - Comorbid asthma (but severe asthma should be considered for a biologic on its own merit) - Failed or contraindicated or unavailable trial of aspirin desensitization if patient has AERD - Steroid side effects/contraindications (reduced bone density, cataract, glaucoma) - Relative costs of available drugs	Major considerations: - Improved quality of life ($\geq 2 \times$ MCID on SNOT-22) and/or $\geq 50\%$ reduction in systemic corticosteroid use (without further surgery) Additional considerations: - Significant improvement in nasal obstruction, allowing nasal breathing and refreshing sleep - Reduction in polyp size compared with baseline of ≥ 2 on Meltzer 8-point bilateral grading system - Improvement in sense of smell (at least out of anosmic range) - Improved asthma control

Two major criteria are a *sine qua non* for consideration of biologic use. Additional criteria provide more pressure in cases in which such therapies are cost-limited. A score of 1 point for each of these could be given, followed by a threshold for use in a particular society determined, taking into account the relative costs of the available drugs. Continuation of the biologic should occur only when its efficacy is of clinically significant benefit to the patient and/or society. Change of polyp grade is not a useful measure, whereas upper airway patency and the ability to nose breathe, smell, taste, and sleep well are all useful. Reduction in systemic corticosteroid use is also an important variable. One point could be given for all of the criteria, after which a threshold is determined based on circumstances. This simple system would allow identification of good responders and nonresponders. Collaborative efforts using clinical data and polyp immunohistology might then permit maximally effective future use of biologic tools.

MCID, Minimal clinically important difference.

These results add to the data from the original studies,⁶ suggesting additional improvements beyond 6 months of treatment and no immediate return of symptoms on discontinuation of treatment. Omalizumab is therefore an effective treatment for CRSwNP. The question is when should it, and other biologics, be used? Approximately 2% to 4% of the population have CRSwNP, and these drugs are expensive. Guidelines for biologic use are available. The European Position Paper on Rhinosinusitis and Nasal Polyps 2020¹ concluded that they are indicated in patients with bilateral nasal polyps who had undergone sinus surgery or were not fit for it and met 3 of the following 5 criteria: (1) evidence of type 2 disease (tissue eosinophil counts ≥ 10 /hpf or blood eosinophil concentrations $\geq 250/\mu L$ or total IgE concentration ≥ 100), (2) need for at least 2 courses of systemic corticosteroids per year or long-term (>3 months) low-dose systemic steroids or contraindication to systemic steroids, (3) significantly impaired quality of life defined by a SNOT-22 score of 40 or higher, (4) anosmia on smell test, and (5) comorbid asthma needing regular inhaled corticosteroids. The European Position Paper on Rhinosinusitis and Nasal Polyps steering group additionally identified cutoffs for “severe” CRSwNP, specifically, a Visual Analogue Scale score of 7 or higher, SNOT-22 score of 40 or higher, and NPS of 5 or higher. Similar criteria have typically been used when recruiting participants for clinical trials of biologics in treatment of CRSwNP. Other therapeutic options, such as antileukotrienes, macrolides, and aspirin desensitization in patients with AERD, may be considered before use of a monoclonal in appropriate patients. Recent evidence suggests that dupilumab is cost-effectively used as rescue therapy where needed following aspirin desensitization in AERD.⁷ Occasionally, allergen-specific immunotherapy, which does have long-term posttherapy benefit, may be appropriate in cases in which polyps are allergen-driven, as in central compartment atopic disease.⁸ Concomitant asthma is a factor promoting use of a biologic.

A combined upper and lower airway scoring system is needed, as is a willingness of regulatory authorities to consider both diseases together in future trials.

Other outstanding questions include how best to judge the response to biologics; how long to continue treatment; when or if to combine surgery with biologic use; and of course, which biologic is likely to give the best result. This latter question remains inconclusively answered in asthma and now in CRSwNP, and it is unlikely to be investigated in head-to-head trials. This leaves indirect comparisons and real-world clinical data as the means for answering this question. With regard to the latter, polyp immunopathology, endotype, phenotype, and relevant biomarkers should now be captured wherever biologics are being extensively used. A widely adopted definition of responsiveness is needed to define responder factors and enable accurate choice of future therapy, particularly now that 3 monoclonals (mepolizumab, omalizumab, and dupilumab) have satisfied the US Food and Drug Administration criteria for use in CRSwNP.

Table I gives our ideas on a simple system for decision-making regarding biologic use.

The role of biologics in CRSwNP will evolve and needs continued investigation and monitoring. Widespread use in nationalized health care systems will require evidence of cost-effectiveness. Currently, they are the future of management for severe type 2 upper and lower airway disease. But watch out for other forms of precision medicine, such as Janus kinase-selective inhibitors.⁹ With upadacitinib having shown greater efficacy than dupilumab in atopic dermatitis,¹⁰ might these oral, small molecule inhibitors be the next CRSwNP therapy?

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