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Biologics for chronic rhinosinusitis with nasal polyps (CRSwNP)

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Conflicts of interest

GKS
Honoraria for articles, speaker and advisory boards:
ALK, Bayer, GSK, Meda/Mylan/Viatris, Sanofi-Regeneron, Stallergenes
Lead for BSACI Rhinitis guidelines
Past Chair of EAACI Ethics Committee
Scientific Chief Editor, Rhinology Section, Frontiers in Allergy
Lead for Allergic Rhinitis, EUFOREA
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Nasal polyps, like asthma, have multiple phenotypes, but are rarely malignant. Until recent decades they were the preserve of the ENT surgeon, with operative removal the main therapeutic option. Advances such as the sinus CT scan, the nasendoscope and endoscopic sinus surgery with resulting tissue examination have prompted research which has altered their management, particularly that of chronic rhinosinusitis with nasal polyposis (CRSwNP). This 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). CRSwNP has significant deleterious effects upon quality of life and ability to function via symptoms of nasal obstruction and discharge, reduction in smell, taste and sleep quality (2).

Pharmacotherapy is now 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, whilst use of oral corticosteroids can both reduce polyp size and restore olfaction temporarily. None of these 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 surgeries. These include, but are not limited to, phenotypes of CRSwNP such as AERD, allergic fungal rhinosinusitis, and eosinophilic granulomatosis with polyangiitis, EGPA. CRSwNP can be associated with asthma, often severe, with similar underlying eosinophilic pathology (1,2), including type 2 innate lymphocytes (ILC2s) (3).

A more recent advance - the development of monoclonal antibody drugs - is set to have a major impact on the treatment of CRSwNP, as it has already begun to do for asthma. These biological 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 FDA. Monoclonals directed against IgE (omalizumab) and the IL-4 receptor alpha subunit (IL-4Rα), common to both IL-4 and IL-13 receptors (dupilumab), also reduce nasal polyp size and symptoms, with studies of others directed against TSLP awaited.

In the current edition of the Journal, Gevaert and colleagues (5) report on an open-label extension evaluating efficacy, safety and durability of responses to omalizumab in adults with CRSwNP who had completed the double-blinded POLYP 1 and 2 trials (6). Two hundred and forty nine of 265 participants from the original study either continued 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, moderate or severe nasal congestion, and SNOT-22 scores of ≥20; 59% of participants had undergone one or more sinus surgeries. 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 24-52, suggesting 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, though not to pre-trial levels by week 72. Extrapolation of the data suggests a prolonged, rather than a permanent, disease-modifying effect.

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

Asthma, mostly mild to moderate, was present in 57.0% of patients. AQLQ improvement at week 52 just exceeded the MCID (0.5 points) in patients who switched to omalizumab from placebo (0.52 points) and was higher (0.95 points) in those who continued omalizumab, suggesting 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).

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. Omalizumab is, therefore, an effective treatment for CRSwNP. The question is when should it, and other biologics, be used? Approximately 2-4% of the population suffer with CRSwNP and these drugs are expensive. Guidelines for biologic use are available. EPOS 2020 (1) concluded that they are indicated in patients with bilateral nasal polyps who had undergone sinus surgery or were not fit for it, and met three of the following five criteria: 1. evidence of type 2 disease (tissue eosinophils ≥ 10/hpf or blood eosinophils ≥ 250/microliter or total IgE ≥ 100); 2. need for at least two 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 SNOT-22 ≥ 40; 4. anosmia on smell test; 5. comorbid asthma needing regular inhaled corticosteroids. The EPOS steering group additionally identified cut offs for ‘severe’ CRSwNP: a visual analogue scale, VAS ≥ 7, SNOT-22 ≥ 40 and nasal polyp score, NPS ≥ 5.

Similar criteria have typically been used when recruiting participants for clinical trials of biologics in CRSwNP. Other therapeutic options such as anti-leukotrienes, macrolides, and aspirin desensitization in AERD patients, 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 post therapy benefit, may be appropriate where polyps are allergen- driven, as in central compartment atopic disease (8). Concomitant asthma is a factor promoting biologic use. A combined upper and lower airway scoring system is needed, plus 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/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 CRSwNP and is unlikely to be investigated in head- to- head trials. This
leaves indirect comparisons and real-world clinical data as the means of answering this question. With regards 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 three monoclonals (mepolizumab, omalizumab and dupilumab) have satisfied FDA criteria for use in CRSwNP. Table 1 gives our ideas on a simple system for decision – making re biologic use.

The role of biologics in CRSwNP will evolve and needs continued investigation and monitoring. Widespread use in nationalised health care systems will require evidence of cost- effectiveness. They are the current future of management for severe type 2 upper and lower airway disease. But watch out for other forms of precision medicine, such as JAK-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?

REFERENCES


5. Gevaert P, Saenz R, Corren J, Han JK, Mullol J, Stella E et al. Long-term efficacy and safety of omalizumab for nasal polyposis in an open-label extension 2 study. JACI 2021

Legend to Table 1.

SUGGESTED CRITERIA FOR BIOLOGICS IN CRSwNP

Two major criteria are a sine qua non for consideration of biologic use. Additional ones provide more pressure where such therapies are cost-limited. A score of one point for each
of these could be given, then a threshold for use in a particular society determined, taking into account the relative costs of available drugs.

Biologic continuation should occur only when its efficacy is of clinically significant benefit to the patient/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 all are. Reduction in systemic corticosteroid use is also an important variable. One point could be given for all of the criteria and again a threshold decided upon based on circumstances.

This simple system would allow identification of good- and non-responders. Collaborative efforts using clinical data and polyp immunohistology might then permit maximally effective future use of biologic tools.
Table 1: Suggested considerations for using biologics in CRSwNP

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