

Rostrum

The Choice of Biologics in Patients with Severe Chronic Rhinosinusitis with Nasal Polyps

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Patients with severe chronic rhinosinusitis with nasal polyps represent an unmet clinical need in terms of recurrent disease despite current medical and surgical therapy. Targeting type 2 inflammatory cytokines (IL4/5/13) appears to be a promising therapeutic approach for such patients akin to what has already been seen in severe asthma. An indirect comparison from phase 3 placebo-controlled trials has shown relative improvements in the coprimary end point of nasal polyp score (NPS) ranging from a 15% reduction (−0.8 units) with mepolizumab, 18% with omalizumab (−1.14 units), and 35% (−2.06 units) with dupilumab. This trend was mirrored by relative improvements in health status with the 22-item Sinonasal Outcome Test score showing a 21% reduction (−13.7 units) with mepolizumab, 27% (−16.1 units) with omalizumab, and 43% (−21.1 units) with dupilumab, all exceeding the minimal clinically important difference of 8.9 units. All biologics improved the coprimary end point of nasal airway blockage and also reduced the need for rescue medical and/or surgical polypectomy. We advocate performing real-life studies looking at the response to biologics in patients who are at increased risk for disease recurrence, including initial optimal medical and surgical polyp clearance before commencing biologics. © 2021 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2021;■:■-■)

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The emerging role of biologics for the treatment of severe chronic rhinosinusitis with nasal polyps (CRSwNP) has stimulated considerable interest among allergists and surgical rhinologists alike. Conventional nonsurgical management involves using oral corticosteroids (OCS) to induce medical polypectomy followed by maintenance high-dose intranasal corticosteroids. Surgical treatment of CRSwNP comprises debulking polypectomy often using a microdebrider along with functional endoscopic sinus surgery to create patent sinus cavities, improve ostiomeatal complex drainage, and allow better topical drug delivery. However, a large proportion of patients often relapse despite such medical or surgical intervention. Type 2 inflammation is the commonest endotype in Europe and the USA associated with severe CRSwNP including the presence of blood or tissue eosinophilia, raised specific immunoglobulin E (IgE) or positive allergen skin prick, elevated fractional exhaled nitric oxide (FeNO), and the presence of asthma and aspirin-exacerbated respiratory disease.¹

There is an unmet need for biologics that target type 2 inflammatory pathways to improve disease control and reduce the need for rescue medical and surgical polypectomy, as well as to attenuate the systemic burden of recurrent OCS exposure. Corticosteroid-sparing effects of biologics assume even greater relevance in patients who have concomitant severe asthma and CRSwNP.²

PHASE 3 BIOLOGIC TRIALS IN CRSwNP

It therefore seems timely to appraise the data from recent phase 3 placebo-controlled trials that have evaluated type 2 biologics including anti-interleukin receptor 4 alpha (IL4 α) with dupilumab (SINUS 24 and SINUS 52 over 24 and 52 weeks), anti-IgE with omalizumab (POLYP 1 and POLYP 2 both over 24 weeks), and anti-IL5 with mepolizumab (SYNAPSE over 52 weeks), dupilumab, and omalizumab having already been approved for CRSwNP.³⁻⁵

All of these trials followed a similar pattern in employing an initial run-in period with patients taking intranasal mometasone furoate 400 μ g daily to establish a baseline, followed by randomization to subcutaneous injection of either active biologic or placebo for 6 to 12 months while continuing with intranasal mometasone. However, this may not reflect current best clinical practice in terms of reducing nasal polyp size before biologic therapy, and therefore the baseline endoscopic nasal polyp score (NPS) is likely to be artificially high. A higher baseline would in turn result in relatively greater response to subsequent biologic therapy in terms of there being more room for improvement.

For example, in our Tayside Rhinology Mega-Clinic, we use oral prednisolone 25 mg once daily for 2 weeks along with antibiotics if required, followed by fluticasone propionate 400 μ g or

Abbreviations used

CRSwNP- Chronic rhinosinusitis with nasal polyps

FeNO- Fractional exhaled breath nitric oxide

IgE- Immunoglobulin E

IL4- Interleukin 4

IL5- Interleukin 5

IL13- Interleukin 13

MCID- Minimal clinically important difference

NPS- Nasal polyp score (0-8)

OCS- Oral corticosteroid

SNOT-22-22-item Sinonasal Outcome Test (0-110)

UPSIT- University of Pennsylvania Smell Identification Test (0-40)

budesonide 1000 µg nasal drops twice daily for the first 3 months, reducing to a once daily maintenance dose thereafter. To illustrate this point, a study by Vaidyanathan et al⁶ from Dundee was performed in patients with severe CRSwNP where there was a 38% greater relative reduction in endoscopic NPS from 6.3 to 3.9 after 2 weeks of initial prednisolone versus placebo before fluticasone propionate, and a 34% reduction in NPS for initial prednisolone versus placebo when both groups received subsequent fluticasone propionate 800 µg for 3 months. In addition to reducing nasal polyp size, 2 weeks of OCS improves underlying ostiomeatal complex patency.⁷ This in turn demonstrates that using such a sequential regimen of systemic and topical corticosteroid is better than topical corticosteroid alone in terms of shrinking nasal polyps. In other words, the observed magnitude of reduction in NPS in these biologic trials is likely to have been enhanced due to an artificially elevated baseline after run-in while taking intranasal corticosteroid alone. In another study comparing methylprednisolone 100 mg and placebo over 3 weeks, there was a 37% relative reduction in NPS from 6.0 to 3.8 in patients with severe CRSwNP.⁸

The NPS that is scored from 0 to 8 was used as a coprimary end point in all of these biologic trials.³⁻⁵ The main strength of all of these trials was the use of independent blinded central reading of the NPS from endoscopy videos to avoid any observer bias. To try and put these results into clinical context, an indirect comparison of NPS (Table I) showed that the smallest mean percentage reduction in NPS occurred with mepolizumab at 15% (SYNAPSE) and the largest with dupilumab at 35% (SINUS 24) with omalizumab in between at 18% (POLYP 1). The mean baseline NPS in the SYNAPSE trial with mepolizumab was 0.5 lower than in SINUS 24/52 trials with dupilumab, which is unlikely to account for a 2-fold relative difference in magnitude of NPS reduction. Dupilumab was the only biologic to consistently improve mean NPS by more than 1.0 unit in both phase 3 trials. In a *post hoc* responder analysis, the relative proportion of overall patients achieving ≥1 point improvement in NPS versus placebo was 49% for omalizumab, 44% for mepolizumab, and 91% for dupilumab.

All trials showed significant improvements in the nasal obstruction score as a coprimary end point, although this has not been validated in terms of having an established minimal clinically important difference (MCID) and is therefore more difficult to interpret. The 22-item Sinonasal Outcome Test (SNOT-22) score, which was used as a secondary outcome in all of the trials, measures disease specific quality of life with a score

of 0-110. Pointedly, the mean absolute change from baseline exceeded the MCID of 8.9 units with all 3 biologics (Table I). The SNOT-22 score followed the same numerical trend as the NPS in terms of the lowest change occurring with mepolizumab (−13.7 units), the greatest with dupilumab (−21.2 units), and omalizumab (−16.12 units) in between. It is important to appreciate that such indirect comparisons do not take into account the different trial inclusion criteria, although essentially it appears that the severity of the disease as NPS at baseline was broadly similar across the various trials. Notably, the SYNAPSE trial with mepolizumab was the only one that required patients to have at least 1 surgery in the past 10 years as an inclusion criterion. A formal meta-analysis would be informative to confirm putative differences in efficacy between biologics across the various phase 3 trials especially because head-to-head randomized controlled trials are unlikely to be performed in the near future.

The greater objective and subjective responses to dupilumab versus either mepolizumab or omalizumab might reflect its effect on the type 2 pathway by blocking signaling of IL4 and IL13, suppressing levels of IgE and FeNO, and in turn suggesting perhaps a more broad spectrum mode of action.^{9,10} Pointedly, all 3 biologics appeared to reduce the need for rescue medical or surgical polypectomy during the trials. Impaired olfaction is often troublesome for patients with CRSwNP due to disease in the olfactory cleft area and can be objectively assessed using the University of Pennsylvania Smell Identification Test (UPSIT) scored between 0 and 40 with a higher value reflecting a better sense of smell. A value ≤18 reflects anosmia and 19-25 severe hyposmia. The pooled treatment response was a change of 3.9 units from a baseline of 13.2 for omalizumab in POLYP 1/2 for UPSIT and 10.6 from a baseline of 14.1 for dupilumab in SINUS 24/52 (Table II), in keeping with the greater NPS reduction observed with dupilumab. *Post hoc* responder analysis showed the proportion of patients with anosmia with dupilumab decreased by 50% in SINUS 24 and by 49% in SINUS 52, with almost no change observed in the placebo group. In some respects, the response seen in the SYNAPSE trial with mepolizumab might be considered as being unexpected because dexamipexole, a drug that depletes blood and tissue eosinophils, has no effect on nasal polyp size or symptoms in CRSwNP.¹¹

Another key point to make is that only the SINUS 24/52 trials with dupilumab performed computed tomography imaging to objectively demonstrate improvements in the degree of underlying CRS by measuring the Lund-Mackay scores at baseline and after treatment. In this regard, measuring the NPS at endoscopy can be considered as representing the tip of the CRSwNP iceberg with imaging measuring the underlying CRS burden. It would therefore be pertinent to know whether improvements in endoscopy and imaging are concordant given the smaller magnitude of changes in NPS seen with mepolizumab and omalizumab.

TYPE 2 ENDOTYPE AND RESPONSE

Real-world head-to-head comparisons are required in severe CRSwNP to establish which particular type 2 endotypes predict the best response to biologics. In SYNAPSE, there was no significant interaction between baseline blood eosinophil

TABLE I. Phase 3 trials comparing type 2 biologics versus placebo where endoscopic NPS (0-8) was the coprimary end point and SNOT-22 (0-110) was a secondary outcome

Trial	SYNAPSE	POLYP 1	POLYP 2	SINUS 24	SINUS 52
Drug	Mepolizumab	Omalizumab	Omalizumab	Dupilumab	Dupilumab
Baseline NPS	5.5	6.25	6.25	5.94	6.09
Delta NPS	−0.8	−1.14	−0.59	−2.06	−1.80
% change	15	18	9	35	30
Baseline SNOT-22	64	60	60	49	51
Delta SNOT-22	−13.7	−16.1	−15.0	−21.1	−17.4
% change	21	27	25	43	34

MCID, Minimal clinically important difference; NPS, nasal polyp score; SNOT-22, 22-item Sinonasal Outcome Test.

Values are depicted for the absolute delta response from baseline with active drug versus placebo and for the % response (as delta/baseline). The absolute change in SNOT-22 exceeded the MCID of 8.9 with all biologics.

TABLE II. Phase 3 trials comparing type 2 biologics versus placebo where the UPSIT (0-40) was a coprimary end point in SYNAPSE (performed only in Canada, UK, and USA) or a secondary end point in POLYP 1, POLYP 2, SINUS 24, and SINUS 52

Trial	SYNAPSE	POLYP 1	POLYP 2	SINUS 24	SINUS 52
Drug	Mepolizumab	Omalizumab	Omalizumab	Dupilumab	Dupilumab
Baseline UPSIT	N/A	13.4	13.0	14.6	13.6
Delta UPSIT		3.8	3.9	10.6	10.5
% change		28	30	73	77
Baseline Lund-Mackay	N/A	N/A	N/A	19	18
Delta Lund-Mackay				−7	−5
% change				−37	−28
Need for medical polypectomy	−42%	−63%		−74%	
Need for surgical polypectomy	−57%	−84%		−83%	

UPSIT, University of Pennsylvania Smell Identification Test.

Computed tomography scoring (Lund-Mackay 0-24) was a secondary end point in SINUS 24 and SINUS 52 (coprimary end point in Japan for SINUS 24). Values are depicted for the absolute delta response from baseline with active drug versus placebo and for the % response (as delta/baseline). Also presented is relative reduction in requirement for rescue medical or surgical polypectomy where information was available. In SINUS 24/52 and POLYP 1/2, the overall medical and surgical polypectomy rates are presented.

counts and either the subsequent NPS or nasal obstruction score in response to mepolizumab, despite the latter markedly reducing blood eosinophils.⁴ Chan et al¹² observed a disconnect with mepolizumab in terms of improvements in asthma control but not NPS or sense of smell in patients with severe eosinophilic asthma and CRSwNP. We would be intrigued to know if elevated levels of FeNO, an IL13 specific type 2 biomarker, might be predictive of a better response to dupilumab in CRSwNP as has already been shown to the case in severe asthma.¹⁰ By the same token, perhaps elevated FeNO levels might portend a suboptimal response to mepolizumab in CRSwNP despite suppression of blood eosinophils, indicating putative IL13 escape in such cases.¹³ Indeed, the interplay of type 2 cytokines in patients with comorbid severe asthma and CRSwNP might help to elucidate which patients show optimal improvements in upper and lower airway disease control. Another possibility is that biologics such as dupilumab might beneficially modify the sinus microbiome as has been shown in the skin in patients with atopic dermatitis.¹⁴ We believe from a pragmatic point of view that it makes sense to tailor treatment according to the underlying endotype and mode of action. For example, in patients with asthma and CRSwNP, one might choose mepolizumab in eosinophilic patients where asthma was the main problem, and in patients with raised FeNO with asthma and CRSwNP, one might use dupilumab.

CONCLUSIONS AND THE WAY FORWARD

In summary, currently available type 2 biologics already approved for asthma appear to be also effective in CRSwNP. An overall indirect comparison of phase 3 trials suggests a better objective response to dupilumab in CRSwNP, although such putative differences in efficacy would require more formal confirmation by meta-analysis. The phase 3 WAYPOINT trial (NCT04851964) is currently investigating the effects of tezepelumab in severe CRSwNP, a monoclonal antibody targeting the alarmin thymic stromal lymphopoietin in turn blocking signaling of IL4, IL5, and 13, resulting in suppression of FeNO, eosinophils, and IgE. Tezepelumab has recently been shown in the phase 3 NAVIGATOR trial to reduce exacerbations in severe uncontrolled asthma in both type 2 high and low patients.¹⁵ Further clarity is required in terms of which endotypes predict a better response to a particular biologic in CRSwNP and whether there is concordance with the treatment response in patients who have concomitant severe asthma. We would also like to see real-life studies looking at the response to biologics in patients with high type 2 biomarkers, where biologics are commenced after initial medical and surgical polyp clearance.¹ This in turn will require some joined up thinking between physicians and surgeons who manage comorbid patients with refractory severe CRSwNP and associated severe asthma. With this in mind, multidisciplinary clinics are required with a physician and surgeon both present to facilitate a one stop visit to

decide on optimal unified airway management strategies to improve the patient journey.¹⁶ Finally, we would also like to see the development of a composite unified airway score to better reflect the overall disease burden in patients with asthma and CRSwNP.

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