

REVIEW ARTICLE

Updates in biologic therapy for chronic rhinosinusitis with nasal polyps and NSAID-exacerbated respiratory disease

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Abstract

Chronic rhinosinusitis with nasal polyps (CRSwNP) associated with type 2 inflammation and non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD) can be difficult to control with standard medical therapy and sinus surgery. In this group, biologicals are potentially promising treatment options. The phase III clinical trials for omalizumab, dupilumab, mepolizumab and benralizumab in CRSwNP have demonstrated favourable outcomes. Moving forward, direct comparisons among biologicals, refining patient selection criteria for specific biologicals, determining optimal treatment duration and monitoring long-term outcomes are areas of emerging interest. This review summarizes the clinical evidence from the recent 2 years on the role of biologicals in severe CRSwNP and N-ERD, and proposes an approach towards decision-making in their use.

KEYWORDS

biologicals, chronic rhinosinusitis, nasal polyps, NSAID-exacerbated respiratory disease

1 | INTRODUCTION

Chronic rhinosinusitis (CRS) is an umbrella term for chronic inflammation of the nose and paranasal sinuses, which has a wide range of clinical phenotypes. While the complex pathophysiologic mechanisms of CRS are not fully understood, the broad classification of inflammation into type 2 versus non-type 2 inflammation has led to a shift towards endotype-driven treatment in the most recent CRS treatment guidelines.^{1,2} Notably, biologic pharmacotherapies that target specific key players in type 2 inflammation have also been incorporated into these CRS treatment algorithms.

While biologicals are not indicated for all type 2 CRS, they are potentially promising options for subgroups of CRS with nasal polyps (CRSwNP) in which disease control remains suboptimal with

standard therapy. One of these subgroups is non-steroidal anti-inflammatory drug (NSAID)-exacerbated respiratory disease (N-ERD), which is associated with high rates of polyp recurrence even with systemic corticosteroids and endoscopic sinus surgery (ESS). This review summarizes the literature on biologicals for CRSwNP and N-ERD in the last 2 years and explores a practical approach towards incorporating biological treatment for these patients.

2 | CRS—THE EPITHELIAL BARRIER HYPOTHESIS

The nasal epithelium is the first line of defence against the external environment. Healthy nasal microbiome, consisting mainly of

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Corynebacterium and *Staphylococcus* species, regulates the composition of respiratory tract mucus, which in turn protects the mucosal barrier structure.³ Chronic exposure to various pathogens and environmental toxins can lead to epithelial damage, which over time, results in a leaky, dysfunctional barrier. The epithelial barrier hypothesis proposes that chronic immune responses to organisms and allergens translocated across a leaky barrier are responsible for the development of CRS and possibly certain autoimmune and allergic conditions as well.⁴ In CRS, the mucus is cytotoxic and further disrupts the mucosal barrier.⁵ The normal microbiota is also replaced by mainly *Staphylococcus aureus* and *Pseudomonas aeruginosa* species, which are more likely to be antibiotic-resistant.⁵ The vicious cycle of epithelial insults and abnormal epithelial repair responses culminates in epithelial remodelling, which is a hallmark feature of CRS.

The resultant inflammation in CRSwNP is a predominantly type 2 inflammatory response. This is characterized by eosinophils, T helper 2 (Th2) cytokines IL-4, IL-5 and IL-13, IgE and group 2 innate lymphoid cells. IL-33 and thymic stromal lymphopoietin also drive Th2 cytokine production and sustain type 2 inflammation. However, it is also important to recognize the presence of mixed or untypeable inflammatory patterns.⁶ Patients with mixed, granulocytic CRS also demonstrate pro-inflammatory, innate immunity-associated cytokines and can have an overall inflammatory burden similar to type 2-dominant CRS.⁷ While the current biologicals do not target non-type 2 inflammation, it may be worthwhile addressing this group in future translational studies.

3 | NSAID-EXACERBATED RESPIRATORY DISEASE

N-ERD is characterized by a triad of CRSwNP, asthma and hypersensitivity to cyclooxygenase-1 inhibitors, including aspirin and NSAIDs. Its prevalence is about 10% in CRSwNP and 14% in severe asthma.⁸ N-ERD encompasses two pathophysiologic states. The first is a baseline, chronic, predominantly eosinophilic airway inflammation that manifests as asthma and CRSwNP. The second is an acute NSAID hypersensitivity reaction, which typically starts with nasal symptoms within 30–180 minutes of NSAID ingestion followed by bronchoconstriction.⁹ NSAIDs inhibit the cyclooxygenase (COX)-1 pathway and dysregulate the arachidonic acid metabolic pathway. The result is a reduction in anti-inflammatory prostaglandin E2 and overproduction of pro-inflammatory eicosanoids, such as cysteinyl leukotrienes and prostaglandin D2.

The diagnosis of N-ERD is established by clinical history and a positive aspirin challenge test. The oral aspirin provocation test is the gold standard in diagnosing NSAID hypersensitivity. However, it has a risk of anaphylaxis, is contraindicated in certain conditions (e.g. uncontrolled asthma, previous anaphylaxis to NSAIDs and gastrointestinal bleeding) and is time consuming. Inhalation and intranasal lysine-aspirin provocation tests are arguably safer and can be conducted in a shorter amount of time, but are less sensitive (73%–87%) and have variable specificity (73%–100%).¹⁰ In vitro tests are

safe, but none are currently able to reliably diagnose N-ERD with a high degree of probability. A recent systematic review and meta-analysis found that urinary leukotriene E4 (LTE4) could potentially identify NSAID intolerance among asthmatic patients, although further studies are needed to standardize normative values.¹¹ Artificial neural networks, a form of machine learning technique, have also been used to predict N-ERD by recognizing patterns based on clinical characteristics, sputum cell phenotypes and eicosanoid levels in induced sputum supernatant and urine. Compared with the oral challenge test, this algorithm reported higher sensitivity (94% vs. 89%) but lower specificity (73% vs. 93%) in predicting a diagnosis of N-ERD.^{12,13}

The standard care for CRSwNP in N-ERD patients includes NSAID avoidance, corticosteroids, ESS and aspirin therapy after desensitization (ATAD).^{14,15} Corticosteroids inhibit the recruitment of the inflammatory cells that are responsible for leukotriene production. However, short-term inhaled and oral corticosteroids do not affect eicosanoid levels, which suggests inadequate targeting of the cysteinyl leukotriene pathway. ESS is effective in rapidly reducing polyp volume and reducing inflammatory burden temporarily, but on its own, it does not stall the underlying pathophysiologic processes. ATAD targets the underlying cysteinyl leukotriene pathway, reduces the chance of nasal polyp regrowth after ESS and may have some benefit on the sense of smell.¹⁶ However, it may not be an option for patients with unstable asthma, and its gastrointestinal side effects can be difficult to tolerate. Biologicals may therefore be attractive options as primary treatment to control symptoms from nasal polyps and asthma, or as adjuncts in achieving aspirin tolerance.

4 | BIOLOGICALS FOR CRSwNP

4.1 | i) Anti-IgE

Omalizumab is a monoclonal antibody directed against immunoglobulin E (IgE) (Figure 1). It inhibits IgE from binding to high-affinity receptors on basophils, eosinophils and mast cells. It also downregulates IgE-receptor expression on these effector cells and IgE-CD23 interactions on B cells, which further reduces IgE production and Th2 cell differentiation. Omalizumab has been used in allergic asthma and chronic spontaneous urticaria for nearly two decades. As shown in a large systematic review and meta-analysis, it can also be effective in allergic rhinitis, although standard treatment such as intranasal corticosteroid sprays, antihistamines and allergen immunotherapy probably remain the preferred initial options.¹⁷ Additionally, it is used as an adjunct to peanut, milk, multi-food or hymenoptera immunotherapy, where it has been shown to significantly reduce the time to maintenance dose and side effects.^{18–20}

In severe CRSwNP, the phase III POLYP1/POLYP2 clinical trials have demonstrated significantly improved endoscopic, clinical and patient-reported outcomes with omalizumab compared to placebo²¹ (Table 1). Patients who had completed these studies were subsequently followed in an open-label extension study, in which patients

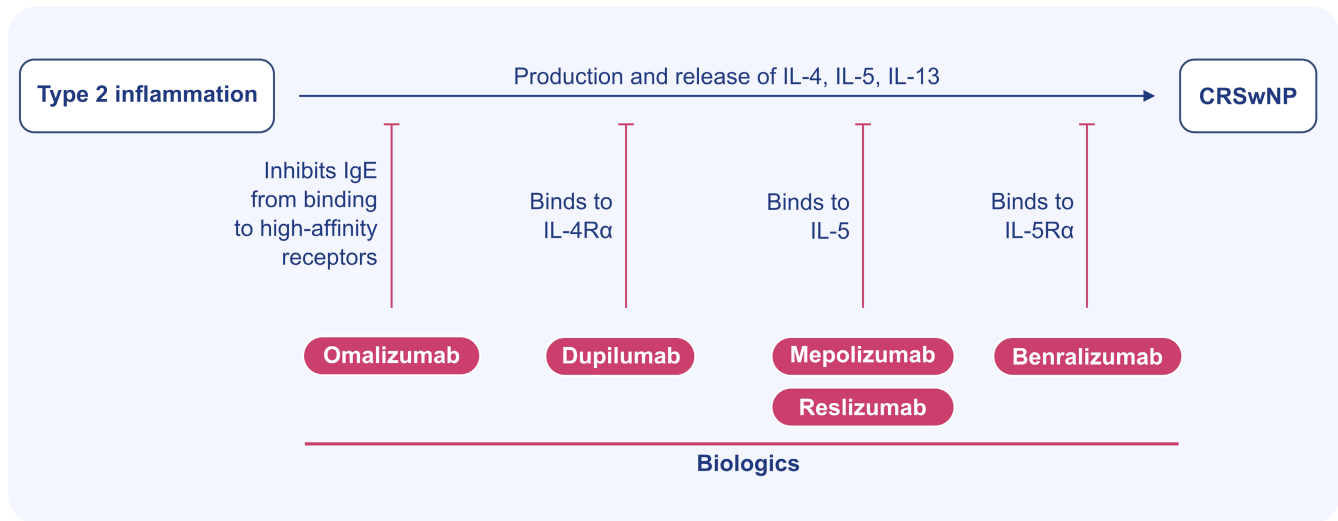


FIGURE 1 Biologics approved for CRSwNP

continued omalizumab, or switched from placebo to omalizumab, for 28 weeks and were followed for a further 24 weeks after discontinuation of omalizumab.²² This study found a further modest improvement in polyp and congestion scores from Week 24 to Week 52, suggesting that the full benefit of treatment was not reached until after 6 months.

A subgroup analysis of the POLYP1/POLYP2 trials reported that the positive clinical outcomes were independent of aspirin sensitivity, asthma status and peripheral eosinophilia.²³ However, the limitations of this analysis included the small N-ERD patient group ($n = 40$), with a mean blood eosinophil count of about $0.3 \times 10^9/L$, which was not particularly high for a N-ERD population, as well as the heterogeneity of the CRSwNP population in these trials. This makes it difficult to draw any conclusions about omalizumab response in N-ERD patients from the POLYP1/POLYP2 studies.

There are other studies that focus specifically on the N-ERD population (Table 2). A small open-label study comparing omalizumab with ATAD ($n = 16$ in each group) found that after 9 months of therapy, most of the patients on omalizumab had their nasal polyp scores reduce from 3 to 0, compared to those on ATAD, whose nasal polyp scores remained around 3.²⁴ In a crossover study, 16 N-ERD patients were randomized to two treatment phases consisting of 3 months of omalizumab or placebo, with a washout period of at least 18 weeks in between the treatment phases.²⁵ An oral aspirin challenge was performed at the end of each treatment phase. The study found that oral aspirin challenge following 3 months of omalizumab therapy inhibited respiratory symptoms and urinary LTE4 overproduction, which enabled 62.5% of participants to achieve aspirin tolerance of up to 930 mg.²⁵ A small clinical report with a high proportion of N-ERD patients found that high blood eosinophils, rather than IgE, predicted greater improvements in symptom scores after 16 weeks of omalizumab.²⁶ As N-ERD typically has high blood eosinophils compared to other CRSwNP subtypes, it is possible that omalizumab may benefit N-ERD patients. This will need to be verified with further studies.

There is interest in the role of IgE in cancer immune surveillance, due to a possible link between absent or very low serum IgE and the risk of malignancy.²⁷ A recent disproportionality analysis of the World Health Organization's global database of individual case safety reports found that omalizumab increased the risk of incident cancer by about two-thirds.²⁸ The association was apparently particularly strong for breast and lung cancer. However, it is important to note that this form of analysis is exploratory in nature and does not quantify true risk. These findings will need to be confirmed with follow-up controlled studies to ascertain long-term safety.

4.2 | ii) Anti-IL-4R α

Dupilumab targets the alpha subunit of the IL-4 receptor (IL-4R α). As this is a shared receptor component for IL-4 and IL-13, dupilumab inhibits signalling of both cytokines, which promote Th2 differentiation and IgE class switching in B cells. Dupilumab is also approved for adults with moderate-to-severe atopic dermatitis, moderate-to-severe eosinophilic asthma and oral steroid-dependent asthma.

The phase III LIBERTY NP SINUS-24 and SINUS-52 studies demonstrated that dupilumab significantly improved nasal polyp, nasal congestion, smell and Lund-Mackay scores within 4–8 weeks of treatment.²⁹ The improvement continued up to 52 weeks of dupilumab treatment compared to placebo.²⁹ Its efficacy has also been shown to be reproducible in the real-world setting.³⁰ A post hoc analysis of SINUS-52, stratified by eosinophilic CRS status according to the Japanese Epidemiological Survey of Refractory Eosinophilic Chronic Rhinosinusitis (JESREC) algorithm, showed that dupilumab produced consistent symptom improvement irrespective of the severity of blood eosinophils, suggesting that blood eosinophils may not be suitable biomarkers for predicting dupilumab efficacy in CRSwNP.³¹ In another study reporting quality of life and productivity outcomes from a previous phase IIa trial, 16 weeks of dupilumab added to intranasal corticosteroid spray was found to improve

TABLE 1 Summary of studies on biological therapy in CRSwNP

Study	Type of study	Number of subjects	Study population—key features	Measured treatment effects and key outcomes
Omalizumab				
Gevaert et al. (POLYP 1) ²¹	Phase III trial	Omalizumab (n = 72) vs placebo (n = 66)	• Age 18–75 years • Serum IgE level 30–1500 IU/m • Total NPS ≥5 • NCS ≥2 and weekly mean score >1 • SNOT-22 ≥ 20 • 57.0% with asthma • 27.2% with N-ERD	Treatment arm mean differences (95%CI) at Week 24: • NPS: -1.14 (-1.59 to -0.69) • NCS: -0.55 (-0.84 to -0.25) • SNOT-22: -16.12 (-21.86 to -10.38) • UPSIT: 3.81 (1.38–6.24) Asthma outcomes: • AQLQ: OR 3.7 (1.0–13.7) of achieving MCID
Gevaert et al. (POLYP 2) ²¹	Phase III trial	Omalizumab (n = 62) vs placebo (n = 65)		Treatment arm mean differences (95%CI) at Week 24: • NPS: -0.59 (-1.05 to -0.12) • NCS: -0.50 (-0.80 to -0.19) • SNOT-22: -15.04 (-21.26 to -8.82) • UPSIT: 3.86 (1.57–6.15) Asthma outcomes: • AQLQ: OR 4.0 (1.1–15.3) of achieving MCID
Gevaert et al. ²²	Open-label extension study of POLYP 1 and 2	After 24 weeks of omalizumab or placebo in POLYP 1 and 2, patients (n = 249) received omalizumab for 28 weeks and followed for another 24 weeks	As above	• Continuation of omalizumab from POLYP1 and 2: further improvements in NPS, NCS, SNOT-22, TNSS and UPSIT scores at Week 52. • After omalizumab discontinuation: scores gradually worsened over the 24-week follow-up, but remained improved from pre-treatment levels
Damask et al. ²³	Subgroup analysis of POLYP 1 and 2 by blood eosinophil count, previous sinonasal surgery, asthma and aspirin sensitivity status	Omalizumab (n = 134) vs placebo (n = 131)	As above	Adjusted mean difference in NCS, NPS, SNOT-22, TNSS and UPSIT change from baseline at Week 24 favour omalizumab vs placebo in both cohorts in all subgroups
Dupilumab				
Bachert et al. (LIBERTY NP SINUS-24) ²⁹	Phase III trial	Dupilumab (n = 143) vs placebo (n = 133)	• Age ≥ 18 years • Total NPS ≥5 • NCS ≥2 and weekly mean >1 + either loss of smell or nasal discharge • 59% with asthma • 28% with N-ERD	Least squares mean difference vs placebo (95% CI) at Week 24: • NPS: -2.06 (-2.43 to -1.69) • NCS: -0.89 (-1.07 to -0.71) • SNOT-22: -21.12 (-25.17 to -17.06) • UPSIT: 10.56 (8.79 to 12.34) • LMS: -7.44 (-8.35 to -6.53) Asthma outcomes (pooled SINUS-24 and SINUS-52 [95% CI]): • FEV1: 0.21 (0.13 to 0.29) • ACQ-6: -0.82 (-0.98 to -0.67)
Bachert et al. (LIBERTY NP SINUS-52) ²⁹	Phase III trial	Dupilumab (n = 295) vs placebo (n = 153)		Least squares mean difference vs placebo (95% CI) at Week 52: • NPS: -1.80 (-2.10 to -1.51) • NCS: -0.87 (-1.03 to -0.71) • SNOT-22: -17.36 (-20.87 to -13.85) • UPSIT: 10.52 (8.98 to 12.07) • LMS: -5.13 (-5.80 to -4.46)

TABLE 1 (Continued)

Study	Type of study	Number of subjects	Study population—key features	Measured treatment effects and key outcomes
Lans et al. ³⁰	Prospective cohort study	Dupilumab (n = 131)	- Age ≥ 18 years - with ≥12 weeks follow-up	Mean scores of NPS, SNOT-22, SSIT-12 and ACT improved significantly from baseline to Weeks 24 and 48
Fujieda et al. ³¹	Post hoc analysis of SINUS-52, stratified by eosinophilic CRS status	Dupilumab (n = 290) vs placebo (n = 147)	SINUS-52 cohort	Dupilumab significantly improved NPS, NC and LM scores vs placebo at Weeks 24 and 52, irrespective of ECRS status
Bachert et al. ³²	RCT; secondary outcome data of dupilumab phase IIa trial	Dupilumab (n = 30) vs placebo (n = 30)	- Age 18–65 years - NPS ≥5	Dupilumab (vs placebo): - Proportion of patients with moderate-to-severe CRSwNP decreased from 86.2% to 21.4% (vs 88.0% to 84.2% with placebo) - Significantly greater improvement in SNOT-22, SF-36, and EQ-5D VAS scores. - Significantly lower adjusted annualized mean number of sick leave days (0.09 vs 4.18) and greater improvement in the SNOT-22 item 'reduced productivity'.
Scangas et al. ³³	Cohort-style Markov decision-tree economic model with 36-year time horizon	ESS (n = 197) vs matched dupilumab from SINUS-24 and SINUS-52 (n = 293)	ESS only group: - Mean age 50 years 50% with asthma 20% with N-ERD	Dupilumab (vs ESS) \$536,420.22 and produced 8.95 QALYs (vs ESS: \$50,436.99 and produced 9.80 QALYs) - ESS is cost-effective regardless of the frequency of revision surgery and at any yearly cost of dupilumab above \$855.
Mepolizumab				
Han et al. (SYNAPSE) ³⁸	Phase III trial	Mepolizumab (n = 206) vs placebo (n = 201)	- Age ≥ 18 years - Nasal obstruction VAS score >5 - Overall symptoms VAS score >7 and NPS ≥5 - At least 1 nasal surgery in past 10 years 71.0% with asthma 26.5% with N-ERD	Adjusted difference in median (95% CI) at Week 52 - NPS: -0.73 (-1.11 to -0.34) - Nasal obstruction VAS score: -3.14 (-4.09 to -2.18) - SNOT-22: -16.49 (-23.57 to -9.42) - Loss of smell VAS score: -0.37 (-0.65 to -0.08)
Detoraki et al. ⁴³	Prospective observational	Mepolizumab (n = 44)	- CRSwNP and severe eosinophilic asthma 23% with N-ERD 89% with previous polyp surgery	Pre- and post-treatment scores at 12 months: - Mean SNOT-22: 51.5 vs 29.7 (p < 0.001) - Mean NPS: 2.88 vs 1.77 (p = 0.99) - Mean ACT: 12.1 vs 22.3 (p < 0.001) - Mean %FEV1: 68.1% vs 82.1% (p = 0.044) - Mean blood eosinophils (cells/μl): 863.9 vs 73.7 (p < 0.001)

(Continues)

TABLE 1 (Continued)

Study	Type of study	Number of subjects	Study population—key features	Measured treatment effects and key outcomes
Chan et al. ⁴⁴	Retrospective case series	Mepolizumab (n = 6)	- CRSwNP and severe eosinophilic asthma 50% with N-ERD	Pre- and post-treatment scores (mean treatment duration 9 months): - Mean NPS: 4.7 vs 5.2 - Mean CRS exacerbations requiring OCS in 12 months: 1.2 (unchanged) - ACQ-6: 3.4 vs 0.3 - Mean asthma exacerbations in 12 months: 4 vs 1 - Mean blood eosinophils (cells/μl): 1393 vs 120
Benralizumab				
Bachert et al. (OSTRO) ⁴⁰	Phase III trial	Benralizumab (n = 207) vs placebo (n = 206)	- Age 18–75 years - Total NPS ≥ 5 - Nasal blockage score ≥ 2 - SNOT-22 ≥ 30 67.3% with asthma 29.3% with N-ERD	Least squares mean change vs placebo (95% CI) at Week 56: - NPS: -0.48 (-0.810 to -0.141) - SNOT-22: -7.49 (-13.74 to -1.24) Not statistically significant: - LMS, UPSIT, ACQ-6
Harrison et al. (ANDHI) ⁴¹	Phase IIIb trial on severe eosinophilic asthma - nasal polyposis subgroup	Benralizumab (n = 96) vs placebo (n = 57)	- Age 18–75 years - Severe eosinophilic asthma - Medical history of nasal polyposis	Benralizumab (vs placebo): Greater improvement in SNOT-22 scores (-8.91 [-16.42 to -1.40]) at Week 24
Canonica et al. ⁴²	Post hoc analysis of nasal polyposis subgroup in ANDHI trial	Benralizumab (n = 92) vs placebo (n = 51) completed the study	- Mean age 53 years - Annualized asthma exacerbation rate 3.3 - Mean pre-bronchodilator FEV1 55% predicted - Median blood eosinophilic count 510 cells/μL 71.9% had past nasal polypectomy 40% reported history of sinus surgery	Benralizumab (vs placebo) at Week 24: - Patients with baseline SNOT-22 scores >30: greater improvement in SNOT-22 scores (-10.44 [-19.02 to -1.86]) and higher percentage of responders (OR: 2.99 [1.43–6.24]) Asthma outcomes: - Reduced annualized asthma exacerbation rate by 69% (50–81%) - Greater clinically meaningful improvements in SGRQ total score (-16.7 [-23.3 to -10.2]), FEV1 (+0.32 L [0.06–0.47]) and ACQ-6 (-0.88 [-1.25 to -0.51])
Comparison among biologics				
Agache et al. ⁴⁶	Systemic review	9 RCTs on dupilumab, omalizumab, mepolizumab and reslizumab (n = 1236)	- Adults (≥ 18 years old) with severe CRSwNP, inadequately controlled by standard of care - Follow-up 20–52 weeks	Dupilumab reduces need for surgery or OCS use (moderate certainty, improves smell and quality of life (high certainty)) Omalizumab reduces need for surgery (high certainty), improves smell and quality of life (high certainty) Low certainty for mepolizumab reducing need for surgery, improving smell and quality of life Evidence for reslizumab is uncertain

TABLE 1 (Continued)

Study	Type of study	Number of subjects	Study population—key features	Measured treatment effects and key outcomes
Peters et al. ⁴⁷	Indirect treatment comparison of biologicals and INCS vs placebo	SINUS-24, SINUS-52, POLYP 1 and POLYP 2 cohorts (n = 989)	As per study population in SINUS-24, SINUS-52, POLYP 1 and POLYP 2 trials	Treatment effect (least squares mean change, [95% CI]) at Week 24: Dupilumab had significantly greater improvement vs omalizumab in: • NPS (−1.04 [−1.63 to −0.44]) • NCS (−0.35 [−0.60 to −0.11]) • Loss of smell (−0.66 [−0.90 to −0.42]) • UPSIT (6.70 [4.67–8.73]) • TSS (−1.18 [−1.95 to −0.41]) Dupilumab were significantly more likely to achieve ≥1-point improvement (OR, [95%CI]) vs omalizumab in: • NPS (3.58 [1.82–7.04]) • NCS (2.13 [1.12–4.04])

Abbreviations: %FEV1, ratio of forced expiratory volume in 1 second (FEV1) to predicted FEV1; ACQ, Asthma control questionnaire; AQLQ, Asthma quality of life questionnaire; EQ-5D, 5-dimension EuroQoL general health status VAS; CI, Confidence interval; CRSwNP, Chronic rhinosinusitis with nasal polyposis; ECRS, Eosinophilic chronic rhinosinusitis; ESS, Endoscopic sinus surgery; FVC, Forced vital capacity; INCS, Intranasal corticosteroids; LMS, Lund-Mackay score; MCID, Minimal clinically important difference; MD, Mean difference; NPS, Nasal polyp score; NCS, Nasal congestion score; OCS, Oral corticosteroid; OR, Odds ratio; RCT, Randomized controlled trial; RR, Relative risk; SF-36, Short-form health survey; SGRQ, St. George's respiratory questionnaire; SNOT-22, 22-item Sinonasal outcome test; SSIT-12, Sniffin' Sticks-12 identification test; TNSS, Total nasal symptom score; TSS, Total symptom score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, Visual analogue scale.

overall and disease-specific quality of life, reduce sick leave days and improve work productivity.³²

To investigate the cost-effectiveness of dupilumab versus ESS, a cohort of patients who underwent ESS was compared with a matched cohort from the SINUS-24/SINUS-52 studies using a cohort-style Markov decision-tree economic model.³³ It reported that ESS was more cost-effective than dupilumab (~\$50,000 and 9.80 quality-adjusted life years [QALYs] versus ~\$500,000 and 8.95 QALYs) for upfront treatment of CRSwNP. However, this model quite likely underestimated direct costs from surgery, revision surgery rates, as well as indirect costs from absenteeism, presenteeism and treatment of co-existent asthma.

With regard to N-ERD-related outcomes, a post hoc analysis that pooled data from the SINUS-24/SINUS-52 studies evaluated dupilumab efficacy and safety in N-ERD versus NSAID-tolerant CRSwNP.³⁴ Dupilumab not only significantly improved CRSwNP-related clinical scores at Week 24, it also improved lung function and asthma control in N-ERD patients compared to placebo. The same study also noted that N-ERD patients in the dupilumab group had greater reductions in urinary LTE4 levels from baseline compared to those with NSAID-tolerant CRSwNP. This finding was similar to another small study of 10 patients, which also demonstrated a reduction in urinary LTE4 levels with dupilumab in N-ERD patients.³⁵ This may be due to the role of IL-4R α signalling in inhibiting prostaglandin E2 production, which increases production of cysteinyl leukotrienes and thereby increases urinary LTE4 excretion. The inhibition of both IL-4 and IL-13 may reduce LTE4 production, which could explain the greater reduction in urinary LTE4 from baseline in N-ERD compared to those with NSAID-tolerant CRSwNP.

A real-world, retrospective study of 74 subjects who received biologicals for N-ERD reported that patients on dupilumab benefited from a significant reduction in SNOT-22 scores, corticosteroid

bursts and antibiotic courses, while those on anti-IgE or anti-IL-5/IL-5R α did not see any statistically significant differences in those outcomes.³⁶ It also found that 98% of patients on dupilumab stayed with the treatment, compared with only 26.9%–48.6% who were on other biologicals and remained on them, suggesting that patients tended to perceive symptom improvement with dupilumab and were therefore more likely to continue with it.

With regard to the cost-effectiveness of dupilumab and ATAD in N-ERD, ATAD after ESS was found to be the most cost-effective and required the least incremental cost to avoid additional revision surgeries, followed by salvage dupilumab after failing ATAD after ESS.³⁷ Upfront dupilumab without initial ESS or ATAD was not found to be incrementally cost-effective in any scenario.

4.3 | iii) Anti-IL-5

Anti-IL-5 monoclonal antibodies target eosinophils. Currently, three are available: mepolizumab, reslizumab and benralizumab. Mepolizumab and reslizumab bind to IL-5, reducing the production and survival of eosinophils, whereas benralizumab binds to IL-5R α expressed on eosinophils, leading to direct cell-mediated eosinophil destruction. All three are currently approved for eosinophilic asthma. Reslizumab has yet to complete any phase III clinical trials for CRSwNP at the time of this review.

With mepolizumab, the phase 3 SYNAPSE clinical trial reported significantly improved nasal obstruction and nasal polyp scores while reducing the need for sinus surgery, corticosteroids and blood eosinophil count at Week 52 compared to placebo.³⁸ However, it was also noted that only half of the patients in the mepolizumab group had improvement in nasal polyp scores by 1 point or more. A subgroup

analysis found that compared to placebo, a greater proportion of patients on mepolizumab had improved nasal congestion and nasal polyp scores, regardless of co-morbid asthma or N-ERD status.³⁹ The phase III OSTRO trial for benralizumab found that benralizumab significantly improved nasal polyp score at Week 40 compared to placebo, although the improvement in symptoms and time to first ESS were not significantly different between treatment arms.⁴⁰ In another phase IIIb (ANDHI) trial of benralizumab in patients with uncontrolled, severe eosinophilic asthma, subgroup analysis of patients who had concomitant nasal polyposis (based on medical history alone) showed the benralizumab group had greater improvements in SNOT-22 scores from baseline compared to the placebo group up to Week 24.⁴¹ A post hoc assessment of patients with both severe eosinophilic asthma and nasal polyps found that benralizumab significantly improved SNOT-22 scores and asthma outcomes.⁴²

With regard to real-world evidence, a study of 44 patients with CRSwNP and severe eosinophilic asthma treated with 1 year of mepolizumab reported improvement in CRSwNP symptom and polyp scores, asthma control and blood eosinophil counts, although the improvement in mean nasal polyp scores was not significant.⁴³ A small case series of 6 patients with CRSwNP and concomitant severe eosinophilic asthma treated with mepolizumab for a mean duration of 9 months reported that nasal polyp scores, rhinosinusitis exacerbations requiring oral corticosteroids and subjective sense of smell remained unchanged, even though asthma control did improve significantly and blood eosinophils dropped by over 90%.⁴⁴

The anti-IL-5 clinical trials and real-world studies appear to be weakly indicative of efficacy in CRSwNP, despite eosinophils being thought to be key drivers of type 2 inflammation. Interestingly, a small but robust study of 13 CRSwNP patients who received dexamipexole (a drug found to deplete eosinophils in the treatment of amyotrophic lateral sclerosis) reported that in spite of a 97% reduction in blood and polyp eosinophils, there was no improvement in nasal symptoms or polyp scores.⁴⁵ On the contrary, the LIBERTY NP dupilumab trials showed significant improvement in polyp-related outcomes even though blood eosinophil counts did not change significantly. These findings may suggest that other inflammatory cells and cytokines apart from eosinophils could play important roles in the pathogenesis of nasal polyps. Targeting eosinophils exclusively may be insufficient in achieving clinically important outcomes.

5 | COMPARISONS AMONG BIOLOGICALS AND ATAD

Currently, there are no head-to-head trials that directly compare different biologicals. There are a few systemic reviews and one network meta-analysis that collectively evaluate randomized controlled trials which evaluate single intervention drugs against placebo.^{46–48} These showed with moderate to high certainty that dupilumab ranks among the most beneficial for sinusitis symptoms, health-related quality of life, rescue oral corticosteroids, rescue surgery, polyp size, radiologic severity and adverse events compared to omalizumab,

mepolizumab and ATAD. Dupilumab also appears to be associated with the greatest improvement in smell scores, which may offer mechanistic insights into the pathophysiology of olfactory impairment.⁴⁸ With regard to adverse events, there is little difference among dupilumab, omalizumab, mepolizumab, benralizumab and reslizumab. ATAD appears to be associated with increased adverse events compared to biologicals, although it is clearly the more economic option.⁴⁸ Nevertheless, it is important to bear in mind that these findings are borne from indirect comparisons. Although the individual studies used very similar endpoints, there was also high heterogeneity in terms of study design, study populations and definitions in treatment outcomes, which limit the conclusions that are drawn from this form of analysis.⁴⁹

6 | INCORPORATING BIOLOGICALS INTO CRSwNP TREATMENT

Currently, the biologicals approved by the European Medicines Agency (EMA) and United States Food and Drug Administration (FDA) for treatment of CRSwNP are omalizumab, mepolizumab and dupilumab. This number is likely to grow with the completion of more phase III trials for other biologicals. Until clearer patient subgroup definitions and head-to-head trials are available, clinicians face the dilemma of selecting the most appropriate biological for their patients. We propose the following principles in the choice of biologicals for CRSwNP, which have been adapted from the latest position papers on CRS and the experience of using biologicals in asthma (Figure 2):

6.1 | Step 1: Patient selection

Patients with type 2 CRSwNP should be optimized with standard, appropriate medical therapy first. This is primarily in the form of nasal and/or oral corticosteroids, saline rinses and ESS. In suitable N-ERD patients, ATAD following ESS can be considered. For patients who fail these standard treatments, five clinical criteria are taken into consideration before commencing biologicals. They are as follows: evidence of type 2 inflammation, need for systemic corticosteroids, significantly impaired quality of life, significant loss of smell and co-morbid asthma.^{2,50}

6.2 | Step 2: Choosing a biological

To date, the eligibility criteria for biologicals based on published trials are generally quite similar, making them helpful in predicting who are likely to respond to biologicals as a whole, but less so in identifying specific subgroups of CRSwNP who would respond best to a particular biological. Until direct comparisons among biologicals are conducted and biomarkers that guide patient selection have been identified, the choice of biological should take into account other

TABLE 2 Summary of studies on biological therapy in N-ERD

Study	Study type	Study population	Key findings
Omalizumab			
Forster-Ruhrmann et al. ²⁴	Retrospective review	Omalizumab (n = 16) vs ATAD (n = 16)	Omalizumab group: Improved CRS symptom scores, NPS (2.9 to 1.0, p = 0.003), ACT score (16.5 to 20.6, p = 0.005) and FEV1 (80% to 89%, p = 0.040) at 9 months ATAD group: NPS (3.0 to 2.9, p = 0.75), hyposmia domain scores not significantly changed at 9 months
Hayashi et al. ²⁵	RCT, crossover design	N-ERD (n = 16)	- Omalizumab inhibited respiratory tract symptoms and urine leukotriene E4 during oral aspirin challenge 62.5% developed oral aspirin tolerance up to cumulative doses of 930mg in the omalizumab phase
Dupilumab			
Mullol et al. ³⁴	Post hoc analysis of SINUS-24 and SINUS-52 studies	N-ERD on dupilumab (n = 121), N-ERD on placebo (n = 82), CRSwNP without N-ERD on dupilumab (n = 319), CRSwNP without N-ERD on placebo (n = 200)	Treatment effect (least squares mean change vs placebo) at Week 24: N-ERD group on dupilumab: - NPS: -1.89 (p < .0001) - NCS: -1.17 (p < .0001) - SNOT-22: -24.35 (p < .0001) - UPSIT: 10.17 (p < .0001) - LMS: -6.33 (p < .0001) Asthma outcomes: - FEV1: 0.26 (p < .0001) - ACT-6: -0.97 (p < .0001) Greater improvement with dupilumab in patients with N-ERD (vs without N-ERD) for NCS, SNOT-22, TSS and PNIF
Mustafa et al. ³⁵	Prospective cohort study	N-ERD (n = 10)	Improved SNOT-22 score, LMS, ACT score, mini AQLQ, UPSIT, FeNO, total serum IgE, 24-hour urinary leukotriene E4, serum thymus and activation regulated cytokine
Yong et al. ³⁷	Cohort-style Markov decision-tree economic model with 10-year time horizon	- ATAD: received ESS 3–6 weeks before starting ATAD. - Dupilumab (from SINUS-24 and SINUS-52 cohort): therapy started without first receiving ESS	- ATAD after ESS was cost-effective and dominated appropriate medical management - Adding salvage dupilumab was also cost-effective (ICER \$135,517.33) - Upfront dupilumab therapy was not cost-effective in any scenario (ICER \$273,181.32)
Mepolizumab			
Bachert et al. ³⁹	Post hoc analysis of SYNAPSE study by N-ERD, asthma, blood eosinophil count subgroups	N-ERD (n = 108)	Mepolizumab reduced nasal polyp size, nasal obstruction, risk of surgery and use of systemic corticosteroids regardless of N-ERD or asthma status
Comparison among biologics			
Wangberg et al. ³⁶	Retrospective review	N-ERD patients who have been on biologic therapy (n = 74)	Anti-IL-4R α : reduction in median SNOT-22 score, corticosteroid bursts and median number of antibiotic courses for respiratory disease pre- vs post-biologic initiation Anti-IgE or anti-IL-5/IL-5R α therapy: no significant difference in the above outcomes

(Continues)

TABLE 2 (Continued)

Study	Study type	Study population	Key findings
Oykhman et al. ⁴⁸	Network meta-analysis	29 RCTs evaluating dupilumab, omalizumab, mepolizumab, benralizumab, reslizumab, anti-Siglec-8, etokimab and ATAD (n = 3461)	Moderate to high certainty evidence showed that SNOT-22 improved with dupilumab, omalizumab, mepolizumab and benralizumab. Moderate certainty that risk of rescue surgery decreased with dupilumab, omalizumab, mepolizumab and ATAD Moderate to high certainty that dupilumab ranks among the most beneficial for sinusitis symptoms, health-related quality of life, rescue oral corticosteroids and surgery, endoscopic and radiologic scores, and adverse events

Abbreviations: ACT, Asthma control test; ACQ, Asthma control questionnaire; AQLQ, Asthma quality of life questionnaire; ATAD, Aspirin therapy after desensitization; ESS, Endoscopic sinus surgery; FeNO, Exhaled nitric oxide; FEV1, Forced expiratory volume in the first second; ICER, Incremental cost-effectiveness ratio; LMS, Lund-Mackay score; NCS, Nasal congestion score; N-ERD, Non-steroidal anti-inflammatory drug-exacerbated respiratory disease; NPS, Nasal polyp score; PNIF, Peak nasal inspiratory flow; RCT, Randomized controlled trial; SNOT-22, 22-item Sinonasal outcome test; TSS, Total symptom score; UPSIT, University of Pennsylvania Smell Identification Test.

Patient selection	Choice of biological	Treatment response
Type 2 primary diffuse CRS Uncontrolled disease despite - AMT - Treatable traits - OCS - ESS - ATAD in case of N-ERD Criteria - Evidence of type 2 - Low QoL - Anosmia - Prior OCS use - Comorbid asthma	Registered for CRSwNP - Dupilumab - Mepolizumab - Omalizumab Currently no direct comparison Choice of biological based on - Local availability - Local experience - Type of comorbid asthma - Pregnancy - Level of blood biomarkers - Patient preference - Cost	After 16 weeks evaluate - Improved QoL - Improved olfaction - Improved asthma control - Reduction of nasal polyp size - Reduction in OCS use If one or more of the above Continue, reevaluate after 1 year If none of the above - Stop - Consider switching

FIGURE 2 Principles in selection of biologicals and monitoring response. Legend: AMT, Appropriate medical therapy; ATAD, Aspirin therapy after desensitization; CRS, Chronic rhinosinusitis; CRSwNP, Chronic rhinosinusitis with nasal polyps; ESS, Endoscopic sinus surgery; N-ERD, Non-steroidal anti-inflammatory drug-exacerbated respiratory disease; OCS, Oral corticosteroids; QoL, Quality of life

factors. These considerations include co-morbidities, such as eosinophilic asthma, that may derive concurrent benefit from the biological and practical issues, such as dosing schedules, option of home administration, cost, local health economics and patient preference. As such, different healthcare systems are likely to lay down their own respective arbitrary selection criteria. On an individual level, the choice of biological should be a shared decision-making among the specialties involved in the patient's care and the patient per se.

6.3 | Step 3. Monitoring treatment response

Treatment response is evaluated based on five criteria: polyp size, reliance on steroids, asthma exacerbations, sense of smell and quality of life.^{2,50} At 16 weeks, response should be assessed to avoid unnecessary continuation of an ineffective biological (0 of 5 criteria met).² Otherwise, treatment can be continued and re-assessed in 1 year.

Switching biologicals is an option when adverse reactions are encountered or when response is suboptimal. The literature on switching biologicals in CRSwNP is currently in the form of a few case reports,^{51,52} although we may draw from the experience of switching biologicals in asthma. A historical cohort study of over 3500 patients with severe asthma from 11 countries found that the overall rate of discontinuing or switching biologicals was low, at about 10%.⁵³ There have been reported efficacies in switching from omalizumab to mepolizumab,⁵⁴ omalizumab to reslizumab⁵⁵ and mepolizumab to benralizumab⁵⁶ due to suboptimal response with the initial biological. From the pathophysiologic perspective, anti-IL-5 treatment can be effective when omalizumab is not, as IL-5 is upstream of IgE in the inflammatory cascade and eosinophilia is maintained by non-IgE mediated IL-5 pathways. On the contrary, omalizumab has the advantages of being safe in pregnancy⁵⁷ and can be switched to another biological without requiring a washout period.⁵⁴

6.4 | Step 4: Beyond 1 year?

Currently, it is not well-established if the positive outcomes of biologicals in CRSwNP are sustainable upon discontinuation. In the phase III LIBERTY NP study, the cohort that ceased dupilumab at Week 24 saw gradual regression of nasal congestion and polyp scores towards baseline scores over time.²⁹ Similarly, discontinuation of omalizumab after 24 weeks in the POLYP 1/POLYP 2 studies was associated with gradual increase in polyp and congestion scores, although not to pre-trial levels.²² In other type 2 inflammatory conditions, discontinuation of dupilumab for atopic dermatitis resulted in re-initiation of disease in almost 80% of patients.⁵⁸ Cessation of omalizumab after 1 year of treatment for asthma saw a 68% relapse rate in the omalizumab responders.⁵⁹ The COMET trial on long-term mepolizumab in asthmatics reported a 59% asthma relapse and up to fivefold increase in blood eosinophil counts after discontinuation.⁶⁰ In short, biologicals do not appear to have long-term disease-modifying effects after cessation of treatment, and long-term studies on CRSwNP are needed to determine the optimal duration of biological treatment.

7 | CONCLUSIONS

Our understanding of biological treatment in CRSwNP and N-ERD is only the tip of the iceberg. Subtypes of type 2 CRSwNP are likely to exist, given the variable response of type 2 CRSwNP to different biologicals. Until head-to-head comparisons are made, there are currently no strong recommendations to guide the initial choice of biological. This decision should be discussed with all stakeholders involved in the care of the patient, including the patient himself, taking into account co-morbidities, local health economics, practical aspects of dosing, safety and patient preferences.

Future research perspectives:

- Biomarkers to support the selection of specific biologicals and predict therapeutic outcome
- Randomized controlled trials directly comparing biologicals to assess the effectiveness of each biological in CRSwNP
- Evaluate nasal polyp and asthma control as outcomes of biological treatment, specifically in N-ERD populations
- Effect of biologic treatment on acute exacerbation following exposure to NSAIDs in N-ERD populations
- Compare the effectiveness of upfront biological therapy versus ESS in CRSwNP
- Expected duration of biological treatment and sustainability of results after treatment cessation
- Cost-effectiveness of biologicals, including indirect cost savings on treating comorbid asthma
- Strategies to reduce direct costs of biologicals

Major milestone discoveries

- The biologicals omalizumab, mepolizumab and dupilumab are approved for treatment of type 2 CRSwNP and significantly improving symptom, polyp and quality of life scores compared to placebo. Benralizumab has completed phase 3 clinical trials demonstrating effectiveness in treating type 2 CRSwNP.
- Indirect comparisons among biologicals suggest that dupilumab significantly improves nasal polyp scores and sense of smell compared to placebo, and compared to other biologicals, although no firm conclusions can be drawn.
- When patients fail to respond to standard medical treatment, the five clinical criteria that are important in making the decision to use biologicals are evidence of type 2 inflammation, need for systemic corticosteroids, significantly impaired quality of life, significant loss of smell and co-morbid asthma.
- With regard to treatment for N-ERD, aspirin desensitization following ESS, or salvage dupilumab after failing aspirin desensitization is more cost-effective than upfront dupilumab treatment.
- Omalizumab may be switched to another biological, in the event of poor clinical response, without the need for a washout period.

ACKNOWLEDGEMENT

Nil.

CONFLICT OF INTEREST

Sietze Reitsma has acted as consultant for Sanofi Genzyme and Novartis. Wytske Fokkens has been a member of the advisory board of Sanofi, GlaxoSmithK and Lyra Therapeutics. The department of Otorhinolaryngology of the AMC has received grants from ALK, Allergy Therapeutics and Mylan BV. It has participated in clinical trials and a registration database with dupilumab, mepolizumab and omalizumab. De Yun Wang and Xinni Xu declare that they have no conflicts of interest.

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How to cite this article: Xu X, Reitsma S, Wang DY, Fokkens WJ. Updates in biologic therapy for chronic rhinosinusitis with nasal polyps and NSAID-exacerbated respiratory disease. *Allergy*. 2022;77:3593-3605. doi: [10.1111/all.15507](https://doi.org/10.1111/all.15507)