

The role of biologics in chronic rhinosinusitis: a systematic review

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Background: Chronic rhinosinusitis (CRS) refractory to medical and surgical treatment is challenging. It impacts patients' quality of life significantly. The pathophysiology of CRS has some similarities to allergic asthma and allergic rhinitis (AR) and includes eosinophilia, T-helper cell 2 cytokines, and local immunoglobulin E formation. Monoclonal antibody therapy has been used successfully in asthma and AR and more recently in CRS. Our aim was to systematically review the literature and identify the role of monoclonal antibodies (MAbs) in the treatment of CRS with polyps (CRSwNP) and without polyps (CRSSNP), especially with regard to comparability with current medical treatment, efficacy, and risk of complications. In addition, the role of surgery and biologics was evaluated.

Methods: We identified a total of 5341 relevant studies after a comprehensive database search. Six studies met the inclusion criteria, all 6 randomized, controlled trials.

Results: Treatment with omalizumab and mepolizumab demonstrated improvements in endoscopic nasal polyp score (EPS) and symptoms score in patients with CRSwNP when compared with placebo. Reslizumab reduced nasal

polyp size in patients with raised intranasal interleukin-5 levels. Dupilumab treatment resulted in a 70% reduction in EPS compared with 20% in the placebo group ($p < 0.001$). These MAbs target different inflammatory markers involved in the pathophysiology of CRSwNP. None of the studies reported on CRSSNP or combined surgery with biologics. No severe adverse events were reported.

Conclusion: Evidence demonstrates that use of MAbs leads to clinical improvement in CRSwNP. However, further research is required to determine their long-term effects, comparability to other medical treatments, and potential side effects. © 2019 ARS-AAOA, LLC.

Key Words:

chronic rhinosinusitis; immunotherapy; polyposis; quality of life; nasal polyps; biologic therapy; monoclonal antibodies

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Chronic rhinosinusitis (CRS) affects approximately 4.3% to 12.5% of the population worldwide.¹⁻³ The impact it has on quality of life (QOL) can be significant. It is characterized by inflammation in the paranasal sinus that persists for >3 months and may be associated with (CRSSNP) or without (CRSwNP) polyps (Table 1).⁴ The severity of the disease varies between individuals. However,

it is well recognized that those with concomitant asthma or allergic rhinitis (AR) are more severely affected. At present, management strategies have focused on symptom relief. This can range from topical corticosteroids to oral steroids and antibiotics and endoscopic sinus surgery. "Difficult-to-treat" patients are defined as those in whom an acceptable level of control is not achieved despite appropriate surgery, intranasal corticosteroid, and up to 2 courses of antibiotics or systemic corticosteroids in the last year.⁴ Management of these patients can prove challenging. The success in targeting specific immunologic mediators in asthma with monoclonal antibodies (MAbs) has led to an interest in the use of similar biologic treatments for CRS.

CRS pathophysiology

The clinical dichotomization of CRSSNP and CRSwNP originated by identifying inflammation driven by predominantly T-helper 1 cells (Th1) in the former and T-helper 2 cells (Th2) in the latter.⁵ However, further research

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TABLE 1. Clinical definition of rhinosinusitis as per EPOS 2012

Inflammation of the nose and the paranasal sinuses characterized by ≥ 2 symptoms, one of which should be either nasal blockage/obstruction/congestion or nasal discharge (anterior/posterior nasal drip): • With or without facial pain/pressure • With or without reduction or loss of smell	and either Endoscopic signs of: • Nasal polyps and/or • Mucopurulent discharge primarily from middle meatus and/or • Edema/mucosal obstruction primarily in middle meatus and/or • CT changes: mucosal changes within the ostiomeatal complex and/or sinuses
Acute <12 weeks duration	Chronic >12 weeks duration

CT = computed tomography; EPOS = European Position Paper on Rhinosinusitis and Nasal Polyps.

TABLE 2. Summary of the action of MABs

Inflammatory mediator	Drug	Action
IgE: Activates allergic inflammatory cascade	Omalizumab	Anti-IgE MAB; binds to the Fc region of IgE, which reduces circulating IgE and produces extensive anti-inflammatory effects with eosinophilic apoptosis induction; Fc ϵ RI receptor, which binds specific IgE on basophils, mast cells, and dendritic cells, is downregulated with time, leading to a general step-down in overall allergic inflammation
IL-5: Key mediator in chemotaxis, differentiation, activation, and survival of eosinophils	Reslizumab, mepolizumab, brenzilumab	Anti-IL-5 MAB; binds and inhibits IL-5Ra subunit depleting eosinophils.
IL-4: Produced by Th2; class switching of B cells to plasma cells and IgE production; IL-13: Th2 inflammation initiation and amplification	Dupilumab	Anti-IL-4 MAB; targets the IL-4 receptor α subunit to inhibit IL-4 and IL-13 cytokines central to Th2 mediated inflammation.
IL-33: Directly mediates release of disease-associated downstream cytokines (IL-4, IL-5, IL-13), which recruit pro-inflammatory cells (ILC2, Th2)	Etokimab ⁷	Anti-IL-33 MAB; blocks IL-33 function, which impacts activation of dendritic, basophil, and mast cells as well as ILC2 and Th2 cells

IgE = immunoglobulin E; IL = interleukin; ILC = innate lymphoid cell; MAB, monoclonal antibody; Th = T helper.

determined that the immunologic profile is much more complex and different endotypes of CRS exist based on the involvement of specific inflammatory mediators, either at the molecular or cellular level. Both CRSsNP and CRSwNP are associated with asthma, inhalant allergy, and aspirin hypersensitivity.⁶ However, there is a higher prevalence in the CRSwNP phenotype.⁶ Consequently, the evidence for biologics in CRS stems from research done primarily on patients with asthma and AR.

The etiology of CRS is still poorly understood.⁷ Several biologic markers in CRSsNP and CRSwNP have been identified as part of the inflammatory process. Endotypes may be classed on the cells involved, such as the abundance of eosinophils or neutrophils, on TH-cell populations or levels of immunoglobulin E (IgE) or cytokines, including interleukin (IL)-4, IL-5, or IL-13.¹ These markers of the inflammatory process are the targets of treatment with biologics (Table 2). Other cytokines are involved in adaptive immunity in response to infection, as IL-25 and IL-33 enhance allergic inflammation. This, along with superantigens (*Staphylococcus aureus* enterotoxins), leads to gener-

ation of local mucosal IgE and demonstrates a relationship between innate and adaptive immunity.⁸ Innate lymphoid cells (ILCs) also play a role in the inflammatory process and mirror their T-cell counterparts. ILCs are the cells that initiate the immune response to a stressor. ILC2 cells are stimulated by IL-25 and IL-33, leading to the production of IL-13.⁸ Further characterization of these cells may lead to a more well-targeted therapy.

Furthermore, an additional endotype of CRS has been described, as patients who do not possess the bitter taste receptor T2R38 are at increased risk of failed medical treatment and may have an increased need for surgical intervention.⁹

The aim of this systematic review is to examine the evidence regarding use of MABs in the treatment of CRS.

Materials and methods

PubMed, CINAHL, Embase, and the Cochrane Database of Systematic Reviews were utilized to search for studies published in English from the inception of the databases up

TABLE 3. Criteria for article selection

Inclusion	Exclusion
>18 years	Biologic therapy not specified
English language	
Chronic rhinosinusitis	

to January 29, 2018. An initial limited search of PubMed was performed using the terms “chronic rhinosinusitis,” “immunotherapy,” and “outcomes.” Next, additional relevant keywords or index terms were identified and a detailed, and comprehensive search strategy was generated for all included databases (see Appendix). National clinical trial registries (ClinicalTrials.gov, EU Clinical Trials Register, or International Clinical Trials Registry Platform) were also reviewed. Inclusion and exclusion criteria are shown in Table 3. Outcomes were stratified into clinician-reported findings (Lund-Mackay [LM] scores, polyp sizes) and patient-reported outcome questionnaires and biologic markers.

Quality appraisal

Articles that met all inclusion criteria were assessed by 2 independent reviewers (I.Z.I., S.S.-T.K.) for methodologic quality using standardized critical appraisal instruments from the Cochrane Database of Systematic Reviews. Variabilities in appraisals that arose between reviewers were resolved through discussion with a third senior reviewer (E.H.O.).

Data extraction

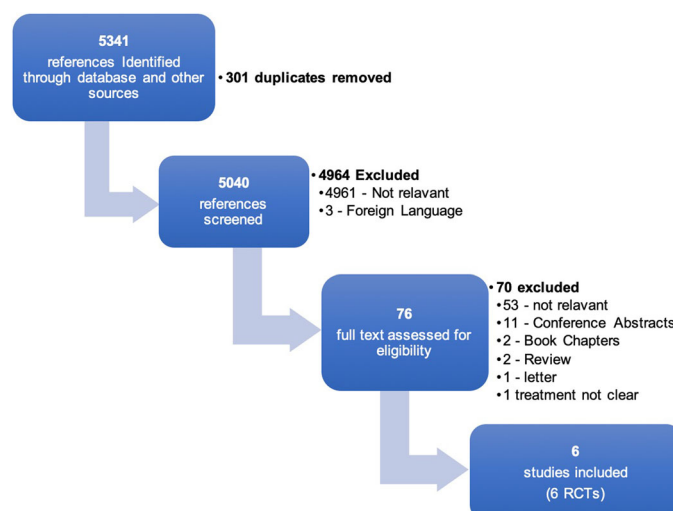
Data were extracted from articles included in the review using Covidence software. The data extracted included study design, patient population, MAb used, treatment doses, and pre- and posttreatment disease severity scores. Study authors were contacted for relevant raw data if they were missing from the published article. Studies were excluded if these data were not available or provided.

Results

After a comprehensive literature search, 5341 articles were identified (Fig. 1). Six studies met the inclusion criteria, all 6 randomized, controlled trials (RCTs).^{2,10–14} Two retrospective cohort studies were excluded as they did not specify the type of biologics used.^{15,16} An overview of the included studies is provided in Table 4. A risk-of-bias assessment is shown in Figure 2.

Endoscopic nasal polyp score

Endoscopic nasal polyp score (EPS) was used as a primary outcome in a number of studies.^{2,11–14} The Meltzer clinical scoring system was used in 5 studies. This system ranges from 0 to 4 for each side, with a maximum score of 8. A higher score indicates worse disease.

**FIGURE 1.** PRISMA diagram. PRISMA, Preferred Reporting Items for Systematic Review and Meta-Analyses.

Anti-IL-4 MAb

Bachert et al¹¹ used video recording to ensure blinding. The data were reported as a least-squares (LS) mean change in bilateral EPS and a change of at least 1 point on the EPS. They reported a statistically significant change in EPS with subcutaneous dupilumab (anti-IL-4 MAb) in comparison to placebo. Blinded treatment was provided on a weekly basis (600-mg loading dose followed by 300-mg weekly doses) for 16 weeks, with a 16-week follow-up. At week 4, the LS mean difference was -1.03 (95% confidence interval [CI], -1.58 to -0.49 ; $p < 0.001$).¹¹ The data were reported as an LS mean change in bilateral EPS and a change of at least 1 point on the EPS. The LS mean change from baseline to week 16 was -0.4 (95% CI, -1.1 to 0.3) in the group with placebo plus mometasone furoate nasal spray (MFNS) and -1.8 (95% CI, -2.5 to -1.2) in the group with dupilumab plus MFNS (LS mean difference, -1.5 ; 95% CI, -2.4 to -0.5 ; $p = 0.002$).¹¹ The change in nasal polyp score was observed in 20% of patients who received placebo vs 70% of those who received dupilumab (odds ratio [OR], 9.5; 95% CI, 2.8 to 31.8; $p < 0.001$).¹¹ The results were similar in patients with CRSwNP and asthma ($p < 0.001$).

Anti-IL-5 MAb

Gevaert et al² compared placebo with a single dose of intravenous (IV) reslizumab (anti-IL-5 MAb) of 1 or 3 mg/kg. The patients in the study had an EPS of 3 or 4 or had recurrent nasal polyposis after surgery. At 12 weeks, there was an improved EPS in 5 of 8 (1 mg/kg) subjects. At 4 weeks, the EPS improved in 4 of 8 (3 mg/kg) subjects in the treatment group. However, the EPS deteriorated in 4 of 8 subjects at 12 weeks after reslizumab in this subgroup. In the placebo group, 3 patients had worse EPS and 1 had improvement. Of the patients who responded to treatment with reslizumab, analysis revealed higher IL-5

TABLE 4. Summary of included randomized, double-blind, placebo-controlled studies

	Gevaert et al ²	Bachert et al ¹¹	Bachert et al ¹²	Gevaert et al ¹⁴	Gevaert et al ¹³	Pinto et al ¹⁰
Treatment	Reslizumab 3 or 1 mg/kg or placebo of a single IV injection	Dupilumab 600 mg SC loading dose, then 15 weekly doses of 300 mg plus MFNS 100 µg in each nostril twice daily or matched placebo for 16 weeks	Mepolizumab 750 mg IV every 4 weeks or placebo (6 in total) plus 1 mg/mL fluticasone propionate at 2 sprays daily	Omalizumab SC every 2-4 weeks vs placebo (max dose 375 mg)	Mepolizumab 2 single IV doses of 750 mg or placebo (28 days apart)	Omalizumab 0.016 mg/kg per IU total serum IgE/mL SC every 4/52 is 4 weeks for 24/52 is 24 weeks vs placebo
Participants	CRSwNP	CRSwNP	CRSwNP	CRSwNP with asthma	CRSwNP	CRSwNP/CRSsNP
No. of patients	24 reslizumab (n = 6) vs placebo (n = 8)	60 dupilumab (n = 30) vs placebo (n = 30)	105 mepolizumab (n = 54) vs placebo (n = 51)	24 omalizumab (n = 16) vs placebo (n = 8)	30 mepolizumab (n = 20) vs placebo (n = 10)	14 omalizumab (n = 7) vs placebo (n = 7)
Cohort with asthma	7 of 8 eslizumab 1 mg/kg, 5 of 8 reslizumab 1 mg/kg, 6 of 8 placebo	16 of 30 dupilumab, 19 of 30 placebo	44 of 54 mepolizumab, 38 of 51 placebo	All patients	10 of 20 mepolizumab, 3 of 10 placebo	All patients
Cohort with allergies	Not specified	18 of 26 dupilumab, 20 of 28 placebo	Not specified	7 of 15 omalizumab, 6 of 8 placebo	10 of 20 mepolizumab, 4 of 10 placebo	Not specified
Aspirin intolerance	Not specified	6 of 30 dupilumab, 6 of 30 placebo	Not specified	8 of 15 omalizumab, 4 of 8 placebo	5 of 20 mepolizumab, 0 of 10 placebo	Not specified

CRSsNP = chronic rhinosinusitis without nasal polyps; CRSwNP = chronic rhinosinusitis with nasal polyps; IV = intravenous; MFNS = mometasone furoate nasal spray; SC = subcutaneous.

Study	Gevaert ²	Bachert ¹¹	Bachert ¹²	Gevaert ¹⁴	Gevaert ¹³	Pinto ¹⁰
Random sequence generation (selection bias)						
Allocation concealment (selection bias)						
Blinding of participants and personnel (performance bias)						
Blinding of outcome assessment (detection bias)						
Incomplete outcome data (attrition bias)						
Selective reporting (reporting bias)						
Other bias						

Key: Unclear, High, Low


FIGURE 2. Risk of bias.

levels in nasal secretions compared with patients who did not respond. All other biologic and nasal scores were comparable between the subjects who responded and those who did not respond. Subsequently, logistic regression analysis revealed that increased nasal IL-5 levels (>40 pg/mL) could predict response to anti-IL-5 treatment (OR, 21.0; 95% CI, 1.5-293.3; $p = 0.009$).²

Bachert et al¹² also compared placebo with 6 doses of 750 mg IV mepolizumab (anti-IL-5 MAb) every 4 weeks. The mean change from baseline in the total EPS showed a significant difference between the placebo and mepolizumab groups from week 9 to week 25.¹² In total, 27 (50%) patients receiving mepolizumab and 14 (27%) patients

receiving placebo improved by ≥ 1 point(s) in total EPS.¹² These findings are supported by those of Gevaert et al,¹³ who also compared mepolizumab (n = 20) with placebo (n = 10). The regimen in their study consisted of two 750-mg IV injections of mepolizumab 28 days apart. The percent improvement in total EPS for mepolizumab was greater than that with placebo: 60% vs 10% (OR, 13.5; $p = 0.018$, Fisher's exact test).¹³ These results are based on the last-observation-carried-forward (LOCF) imputation, as the dropout rate was high. Improved EPS was observed in 12 of 20 patients in the mepolizumab group.

Anti-IgE monoclonal antibody

Omalizumab (anti-IgE MAb) was compared with placebo in patients with CRSwNP, asthma, and total serum IgE levels between 30 and 700 kU/mL. In the study by Gevaert et al,¹⁴ 15 patients received omalizumab and 8 received placebo. The dose was determined by weight and serum IgE levels. Hence, 2 patients received fortnightly treatment, whereas 22 patients received monthly treatment. The total EPS after 16 weeks of treatment compared with baseline was significantly reduced in the omalizumab group (-2.67 , $p = 0.001$), but not in the placebo group (-0.12 , $p = 0.99$).¹⁴ This effect was seen from 8 weeks onward and was statistically significant at 16 weeks ($p = 0.005$).

After 16 weeks, the allergic and nonallergic patients in the omalizumab group both had a decrease in total EPS (-2.57 [$p = 0.03$] and -2.75 [$p = 0.06$], respectively).¹⁴

Pinto et al¹⁰ compared omalizumab with placebo in their RCT. There were 7 patients in each arm of the study. EPS was a secondary outcome measure. There were no significant changes of EPS for either group and the net change across treatments was not significantly different (omalizumab, 0; placebo, -0.5 ; $p < 0.58$).¹⁰

Nasal peak inspiratory flow

Peak nasal inspiratory flow directly measures nasal air-flow during maximal inspiration.¹⁷ After treatment with mepolizumab at week 25, the LS mean nasal peak inspiratory flow (NPIF) was found to be statistically significantly better compared with the placebo group (mean difference, 26.7 ; 95% CI, 3.1 - 50.2 ; $p = 0.027$).¹² This result was similar to the LS mean difference between placebo and dupilumab 33.1 L/min (95% CI, 12.7 - 53.5 L/min; $p = 0.002$).¹¹ In another study, the mepolizumab-treated group also showed an improvement in NPIF compared with baseline ($p = 0.095$) up to 8 weeks after treatment.¹³ However, Pinto et al¹⁰ did not report any statistically significant difference between the placebo and omalizumab groups.

Smell identification tests

The prevalence of CRS-related olfactory loss has been estimated at between 20% and 80%.¹⁸ The University of Pennsylvania Smell Identification Test (UPSIT) and Sniffin' Sticks are both validated instruments to quantitatively measure sense of smell. Pinto et al¹⁰ reported an improvement in UPSIT scores, but this was not statistically significant ($p < 0.31$). Their findings are similar to those of the Bachert et al study comparing mepolizumab vs placebo using Sniffin' Sticks (mean difference, 0.7 ; 95% CI, 20.5 to 1.9 ; $p = 0.233$).¹²

Two further RCTs demonstrated statistically significant improvement in UPSIT scores with immunotherapy. In a comparison of dupilumab vs placebo,¹¹ the LS mean change in UPSIT score was 14.8 (95% CI, 10.9 - 8.7 ; $p < 0.001$). Comparison of omalizumab vs placebo also demonstrated an improvement in UPSIT score¹⁴ ($p = 0.004$).

Radiologic findings

A comparison of placebo and dupilumab demonstrated an LS mean change from baseline to week 16 for the LM CT total score of -8.8 (95% CI, -11.1 to -6.6 ; $p < 0.001$).¹¹ Gevaert et al¹⁴ also reported an improved LM score with omalizumab ($p = 0.04$). The improvement in LM score was significantly better in allergic patients (-2.61 ; $p = 0.04$) compared with nonallergic patients (-0.66 ; $p = 0.75$).

Bachert et al¹¹ reported on the change in percentage of maxillary sinus volume occupied by disease. The LS mean change was -4.2 (95% CI, -13.5 to 5.2) with placebo and -36.4 (95% CI, -44.4 to -28.4) with dupilumab (LS mean difference, -32.2 ; 95% CI, -43.1 to -21.4 ; $p <$

0.001). This demonstrated an improvement in sinus disease radiologically.

Gevaert et al¹³ reported CT scores from 3 different observers. Improvement was seen in $>50\%$ of mepolizumab-treated patients and in $<20\%$ of the placebo group when compared with baseline scans ($p = 0.058$, $p = 0.024$, and $p = 0.049$ for the different raters by using LOCF, Fisher's exact test).

Pinto et al¹⁰ measured the percentage opacification on coronal CT imaging pre- and posttreatment at the level of the osteomeatal unit. In the omalizumab cohort, percentage opacification improved from 76.1% to 60% ($p < 0.043$) over 16 weeks. The change in the placebo group was less significant, from 75.9% to 66.1% ($p < 0.463$). However, the median change across treatment groups was not significant ($p < 0.391$).

Respiratory tests

Bachert et al¹¹ reported an improvement in forced expiratory volume (FEV) in asthmatic patients who received dupilumab compared with placebo (0.2 ; 95% CI, -0.02 to 0.5 ; $p = 0.07$). In another study, there was an improvement in FEV ($p = 0.077$), forced vital capacity ($p = 0.094$), and peak expiratory flow rate ($p = 0.484$) with mepolizumab vs placebo.¹²

Biologic markers

Both Bachert et al^{11,12} and Gaevart et al.^{2,13} assessed blood eosinophil counts in response to treatment. Reslizumab induced a sustainable reduction in blood eosinophil count from 12 hours after administration.² This returned to baseline at 12 weeks and a rebound increase thereafter, which was $>100\%$ in 6 patients from the 1-mg/kg group and in 4 patients from the 3-mg/kg group. Further analysis revealed that only those with IL-5 levels of >40 pg/mL in nasal secretions responded to treatment. The authors concluded that IL-5 and eosinophils played a key role (IL-5 dependent) in 50% of the nasal polyps, whereas in the others eosinophilia may have been dependent on other factors (IL-5 independent). In addition, serum eosinophilic cationic protein (ECP) and secreted IL-5 α decreased with reslizumab compared with placebo for the first few weeks after treatment.

There was also a reduction in eosinophil count when comparing dupilumab + MFNS with placebo + MFNS. This was reported as a difference in percentage change in LS mean of -4.4 (95% CI, -36.1 to 27.2 ; $p = 0.78$).¹¹ This was also statistically significant when measuring total serum IgE ($p < 0.001$) and plasma eotaxin-3 ($p < 0.001$) levels. In contrast, there was no change in plasma or nasal eotaxin levels throughout the study with reslizumab.

In the Bachert et al¹² study, patients receiving mepolizumab demonstrated a reduction in blood eosinophil count from baseline to week 25. This was not seen in the placebo group.¹² At week 8 after treatment with mepolizumab, the treatment group showed a significant

TABLE 5. Quality-of-life markers

Study	Instrument	Quality-of-life results
Bachert et al ¹¹ : subcutaneous dupilumab + MFNS vs placebo + MFNS	SNOT-22, VAS	Improvement in SNOT-22 score from baseline to week 16 in dupilumab group; LSQ difference, -18.1 (95% CI, -25.6 to -10.6), $p < 0.001$; absolute difference for dupilumab vs placebo, LS mean VAS -2.1 (95% CI, -3.7 to -0.6), $p = 0.008$; nasal congestion or obstruction in the morning, -0.7 (-1.1 to -0.3), $p < 0.001$; posterior rhinorrhea in the morning, -0.5 (95% CI, -0.8 to -0.2), $p = 0.002$
Bachert et al ¹² : mepolizumab vs placebo	VAS, SNOT-22, EQ-5D	Improvement in VAS in mepolizumab group, $p = 0.001$; mepolizumab group improvement in rhinorrhea ($p < 0.05$), nasal blockage ($p < 0.01$), mucus in throat ($p < 0.001$), and loss of smell ($p < 0.001$); placebo: week 1, 49.5 (SD, 19.0); week 25, 38.2 (SD, 24.5); mepolizumab: week 1, 51.5 (17.0); week 25, 28.8 (22.0); improvement in the mepolizumab group, $p = 0.005$; no difference between placebo and mepolizumab at 25 weeks
Geveart et al ¹⁴ : omalizumab vs placebo	VAS, SF-36, RSOM-31, AQLQ	Improvement in omalizumab group in nasal congestion ($p = 0.002$), anterior rhinorrhea ($p = 0.003$), and loss of sense of smell ($p = 0.004$); improvement in omalizumab group ($p = 0.02$) but not in the placebo group ($p = 0.75$); improvement in sleep ($p = 0.03$) and general symptoms ($p = 0.01$) in the omalizumab group, no change in placebo group; improved after treatment by 0.27 and 0.81 point, respectively, in the placebo and omalizumab groups; at 16 weeks, the change in omalizumab group was significant, $p = 0.003$
Geveart et al ¹³ : mepolizumab vs placebo	VAS	Reduction from baseline in loss of smell, postnasal drip, and congestion at week 8 was greater in mepolizumab group (not statistically significant); rhinorrhea stayed at the same level; improvement in loss of smell stayed the same (11 months after the last dose), whereas the other symptoms normalized after a period of time in mepolizumab group
Pinto et al ¹⁰ : omalizumab vs placebo	SNOT-20, SF-36	Improvement in SNOT-20 in omalizumab group, -1.05 vs placebo -0.20 , $p < 0.78$; no significant difference between groups apart from vitality score in omalizumab (9.4) and placebo (12.5), $p < 0.05$

AQLQ = Asthma Quality of Life Questionnaire; CI = confidence interval; EQ-5D = EuroQoL 5-Dimension Questionnaire; LS = least squares; MFNS = mometasone furoate nasal spray RSOM-31 = 31-item Rhinosinusitis Outcome Measure; SF-36 = 36-item Short Form-36; SNOT-20 or 22 = 20- or 22-item Sino-Nasal Outcome Test; SD = standard deviation; SOQ = Sinusitis Outcome Questionnaire; VAS = visual analog scale.

reduction in blood eosinophils ($p < 0.001$ for LOCF), serum ECP levels ($p = 0.022$ for LOCF), and serum IL-5Ra levels ($p < 0.001$ for LOCF).¹³

QOL markers

A number of validated QOL markers have been utilized to record the impact of treatment with biologics in patients. These findings are summarized in Table 5. Overall, there was a significant improvement in nasal-specific symptoms as well as in general QOL markers in those receiving MABs.

Complications associated with MABs

Six of the studies reported on adverse events (AEs).^{2,10–14} Gevaert et al² found that 95.8% (23 of 24) of the patients in their study had at least 1 AE. The most common AE reported was upper respiratory tract infection (58.3%, $n = 14$). Of these, 10 patients were from the treatment arms (reslizumab 1 mg/kg [$n = 5$] or 3 mg/kg [$n = 5$]) and 4 in the placebo arm. The number of AEs was similar in another study by Gevaert et al,¹⁴ where 95.7% reported at

least 1 AE, and in the study by Bachert et al,¹¹ in which 25 of 30 placebo group and 30 of 30 dupilumab group patients reported AEs. The common cold appeared significantly more frequently in the omalizumab group compared with the placebo group ($p = 0.02$), but no other significant differences were reported.¹⁴ Furthermore, 1 patient from the placebo group dropped out because of an AE (asthma attack) and 1 patient from the dupilumab group had a fatal lymphoblastic lymphoma 1 year after completing the study. The investigators reported that a relationship between the treatment and the lymphoblastic lymphoma was unlikely.

The most frequently reported AEs in the dupilumab-vs-placebo study were nasopharyngitis (placebo, 33%; dupilumab, 47%), injection-site reactions (7% vs 40%, respectively), and headache (17% vs 20%, respectively).¹¹ Five patients from the placebo group dropped out of the study due to AEs (otitis media, bronchitis, hypersensitivity, headache, hypertension, abdominal pain, and asthma), as did 2 patients in the dupilumab group (constipation, injection site reaction). Although 6 serious AEs (placebo, 4; dupilumab, 2) were reported, none were attributed to the study.

Patients receiving placebo or mepolizumab reported AEs in 81% and 75% of patients, respectively.¹² Investigators assessed that 6% of the placebo group and 12% of the mepolizumab group AEs were drug-related. This led to patients withdrawing from the study (placebo, 12%; mepolizumab, 6%). The most common AEs were headache (placebo, 38%; mepolizumab, 25%), nasopharyngitis (placebo, 23%; mepolizumab, 19%), and oropharyngeal pain (placebo, 8%; mepolizumab, 11%). Gevaert et al¹³ found that 53% ($n = 30$) of patients reported AEs in their comparison of mepolizumab vs placebo. However, the common cold was the most frequently reported AE (mepolizumab group, 25%; placebo group, 10%). Also, there was 1 serious AE (diverticulitis) reported, but it was due to a pre-existing condition and not thought to be linked with biologics. Overall, AEs were more frequent in the mepolizumab group.

In contrast to the aforementioned findings, Pinto et al¹⁰ reported no side effects or AEs. Overall, no serious AE attributed to biologics were reported in any of the studies.

Discussion

The studies included in this systematic review all reported on CRSwNP, with only 1 including CRSsNP. This may highlight the different pathophysiology and treatment paradigms between the 2 phenotypes.

It is increasingly recognized that CRS comprises a spectrum of conditions with distinct clinical presentations and pathogenic mechanisms.¹⁹ Although CRSsNP is recognized as being predominantly neutrophilic Th1 driven and CRSwNP as eosinophilic Th2 (high-cytokine IL-4, IL-5, IL-13) driven, there is some overlap between the different phenotypes and endotypes. CRSwNP in Asian populations is driven by Th17 (raised cytokines IL-6, IL-17, and IL-22, tumor necrosis factor- α). Although there are biologic treatments available targeting cytokines in the Th1 and Th17 pathways (eg, rheumatoid arthritis or osteoarthritis), none have thus far looked at CRSsNP.²⁰

Three studies reported on the use of anti-IL-5 treatment.^{2,12,13} There was a greater improvement in EPS in the treatment groups in all of these studies. In the reslizumab study, the findings were statistically significant in those patients with high intranasal IL-5 levels. These participants were termed “responders.” The highest concentrations of IL-5 were found in the nasal polyp tissue of subjects with nonallergic asthma and aspirin sensitivity, conditions linked to severe tissue eosinophilia.² The levels of intranasal IL-5 also decreased in the responder group and increased in the nonresponder group, which may lead to targeted therapy in these individuals. In an RCT assessing the use of reslizumab in eosinophilic asthma, Castro et al²¹ found that patients with nasal polyps reported a statistically significant improvement in asthma control questionnaire scores in the treatment group when compared with the placebo group (-1 vs -0.1 ; $p = 0.0119$). Dupilumab (anti-IL-4) treatment led to a significant reduction in EPS in CRSwNP with

asthma.¹¹ It also led to a significant reduction in LM score, 22-item Sino-Nasal Outcome Test score, and improvement in UPSIT and self-reported sense of smell in patients without asthma.¹¹ In the same study, 58% of the patients had undergone prior nasal surgery, suggesting there may be a case for use of dupilumab in such patients.¹¹ These data suggest that signaling pathways mediated by IL-4 and IL-13 play a major role in the pathogenesis of CRSwNP, and that blocking these pathways leads to significant clinical benefit.¹¹ Both IL-4 and IL-13 actively promote adaptive Th2 response by activating B cells and local production of immunoglobulins.²² As dupilumab targets a shared α subunit on IL-4 and IL-13, its role in suppressing downstream pathways is significant.

Two trials assessed the effects of anti-IgE treatment (omalizumab).^{10,14} Treatment with omalizumab led to a significant reduction in EPS in one of these studies but not the other. All patients in both studies had asthma, but the Pinto et al¹⁰ study included participants with CRSsNP and CRSwNP. This, along with the smaller sample size in the study, may account for these results. Interestingly, apart from a marginal improvement on CT imaging in the treatment group, there was no improvement in NPIF or QOL measures in this study.

In a retrospective cohort study, Nishioka et al¹⁵ looked at polyp recurrence in both allergic and nonallergic CRS patients. The type of biologic treatment was not defined in their report. However, they concluded that patients with CRS and AR had a higher incidence of polyp recurrence after functional endoscopic sinus surgery. Polyp recurrence in the nonallergic group was 12.4% (21 of 169) compared with 25.8% (17 of 66) for allergic patients ($p < 0.012$).¹⁵

There are no data comparing surgery directly with biologics. The role of biologics in conjunction with or as an alternative to surgery needs to be investigated further. However, advances in understanding the biologics of CRS endotyping are necessary to correctly identify suitable patients. Bachert et al¹² reported that a greater proportion of patients in the mepolizumab group no longer met the criteria for surgery compared with placebo ($p = 0.006$). This is in contrast to findings by Gevaert et al,¹³ where there was a high dropout rate. The reasons for this included the need for rescue medication (mepolizumab group, 5 of 20; placebo group, 3 of 10) and nasal surgery with removal of nasal polyps (mepolizumab group, 4 of 20; placebo group, 3 of 10).¹³ It is important to note that both frequency and duration of treatment with mepolizumab were greater in the Bachert et al study, which may account for the difference.

All studies reported an improvement in radiologic findings and QOL markers with MAb use. The variations in the extent of improvement must be evaluated further. The cost implications and commitment required by participants, both with regard to time and the possibility of receiving placebo while having a condition that impacts QOL, may have a major influence on implementation of larger studies. In the first instance, it would be the “difficult-to-treat”

group that would be the focus of future studies. Our understanding of the pathophysiology will have a significant impact on how MAb treatment is targeted in such patients.

No studies in our review reported severe AEs directly related to MAb use. Malignancy and anaphylactic reactions (0.1%-0.2%) have been linked to omalizumab.²³⁻²⁵ However, a prospective, observational cohort study comparing omalizumab with no omalizumab in patients with moderate-to-severe allergic asthma showed no increased risk of malignancy.²⁶

The data do demonstrate improvement in certain patients. However, identifying which patients would benefit from MAb treatment is still in its infancy. Those patients who are still symptomatic despite current maximal medical therapy and surgical intervention are currently the main focus of treatment with biologics. A multidisciplinary shared airway and immunology approach could possibly identify patients who may require treatment with biologics at an earlier stage in the disease process. This may subsequently have an overall positive impact on the psychological burden of the disease on the patient and the health-care service.

Limitations

The lack of standardization of outcome reporting across the studies makes it difficult to compare studies. A meta-analysis of change in EPS was of particular interest, but due to the differences in reporting this could not be performed. For future studies standardization of reporting outcomes would prevent such an analysis. CRS is a complex disease with patients who have previously undergone either medical or surgical treatment. Thus, the heterogeneity in the patient population may have further biased the cohort

patients in this review. In addition, our review only included studies published in English, and, as a result, eligible studies in other languages may have been overlooked.

The cost of treatment with biologics is also a factor that would limit the use of this treatment. At present, no studies have reported on the cost-effectiveness of monoclonal antibodies in CRS. There are data that showed use of omalizumab and dupilumab in asthma and atopic dermatitis is cost-effective.^{27,28} Larger sample sizes as well as standardization of reporting outcomes in studies would allow us to analyze the health economics of biologics in CRS.

Further research

Currently, there are 2 trials in the recruitment phase in the United States: one looking at the effect of bendralizumab (anti-IL-5) on severe CRS with eosinophilic polyposis and another on reslizumab in CRS with asthma. In the EU Clinical Trials Registry there are ongoing studies looking at omalizumab in CRSwNP. In the International Clinical Trials Registry Platform, there is a trial assessing use of etokimab (anti-IL-33) in CRSwNP.

Conclusion

There is evidence available supporting the use of biologics in CRSwNP. MAbs are well tolerated with no severe AEs. Although our understanding of the biologic processes continues to improve, further categorizing of endotypes is necessary to properly target the use of MAbs. Further research into biologics vs surgery as well as long-term disease control is required. 

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Appendix

Terminology used for database search.

PubMed

Sinusitis[mh] OR Sinus*[tw] OR Sinusitides[tw] OR Chronic rhinosinusitis[tw] OR CRS[tw] OR CRSwNP[tw] OR Nasal polyps[mh] OR Nasal polyp*[tw] OR Nose polyp*[tw] OR Papillom*[tw] Polyps[mh] OR Polyp*[tw] AND

Immunotherapy[mh] OR Immun*[tw] OR Therap*[tw] OR Immunomodulation[mh] OR Immunomodulat*[tw] OR Antibodies, Monoclonal[mh] OR Monoclon*[tw] OR Antibodies[mh] OR Antibod*[tw] OR Immunoglobulins[mh] OR Interleukins[mh] OR Interleukin*[tw] OR Cytokine*[tw] OR IL-5[tw] OR IL-4[tw] OR IL-13[tw] OR Interferons[mh] OR Interferon*[tw] OR Omalizumab[mh] OR Omalizumab[tw] OR Xolair[tw] OR Receptors, IgE[mh] OR IgE[tw] OR Anti-IgE antibodies[mh] OR Anti-IgE[tw] OR Mepolizumab[mh] OR Mepolizumab[tw] OR Reslizumab[mh] OR Reslizumab[tw] OR Benralizumab[mh] OR Benralizumab[tw] OR AMG 282[tw] OR Sialic acid[tw]

AND

Quality of life[mh] OR Quality of life[tw] OR Quality-of-life[tw] OR Health-related-quality-of-life[tw] OR Life quality[tw] OR QOL[tw] OR HRQOL[tw] OR Morbidity[mh] OR Morbidit*[tw] OR Lund-Mackay[tw] OR Polyp size*[tw] OR Visual analog scale[mh] OR Visual analog scal*[tw] OR VAS[tw] OR Total nasal symptom severity[tw] OR TNSS[tw] OR Sinonasal outcome test-22[tw] OR SNOT-22[tw] OR Rhinosinusitis Outcome Measure-31[tw] OR RSOM-31[tw] OR 36-Item Short Form[tw] OR SF-36[tw] OR Peak nasal inspiratory flow [tw] OR University of Pennsylvania Small Identification Test[tw] OR UPSIT[tw]

CINAHL

MH Sinusitis OR TI Sinus* OR AB Sinus* OR TA Chronic rhinosinusitis OR AB Chronic rhinosinusitis OR TI CRS OR AB CRS OR TI CRSsNP OR AB CRSsNP OR MH Nasal polyps OR TI Nasal polyp* OR AB Nasal polyp* OR TI Nose polyp* OR AB Nose polyp* OR TI Papillom* OR AB Papillom* OR MH Polyps OR TI Polyp* OR AB Polyp*

AND

MH Immunotherapy OR TI Immun* OR AB Immun* OR TI Therap* OR AB Therap* OR MH Immunologic factors OR MH Antibodies, monoclonal OR TI Monoclon* OR AB Monoclon* OR

MH Antibodies OR TI Antibod* OR AB Antibod* OR MH Immunoglobulins OR MH Interleukins[mh] OR TI

Interleukin* OR AB Interleukin* OR TI Cytokine* OR AB Cytokine* OR

TI IL-5 OR AB IL-5 OR TI IL-4 OR AB IL-4 OR TI IL-13 OR AB IL-13 OR MH Interferons OR

TI Interferon* OR AB Interferon* OR TI Omalizumab OR AB Omalizumab OR TI Xolair OR

AB Xolair OR TI IgE OR AB IgE OR TI Anti-IgE antibodies OR AB Anti-IgE antibodies OR TI Anti-IgE OR AB Anti-IgE OR TI Mepolizumab OR AB Mepolizumab OR TI Reslizumab OR AB Reslizumab OR TI Benralizumab OR AB Benralizumab OR TI AMG 282 OR AB AMG 282 OR

TI Sialic acid OR AB Sialic acid

AND

MH Quality of life OR TI Quality of life OR AB Quality of life OR TI Quality-of-life OR AB Quality-of-life OR TI Health related quality of life OR AB Health related quality of life OR TI Health-related-quality-of-life OR AB Health-related-quality-of-life OR TI Life quality OR AB Life quality OR TI QOL OR AB QOL OR TI HRQOL OR AB HRQOL OR MH Morbidity OR TI Morbidit* OR AB Morbidit* TI Lund-Mackay OR AB Lund-Mackay OR TI Polyp size* OR AB Polyp size* OR MH Visual analogue scaling TI Visual analog scal* OR AB Visual analog scal* OR TI VAS OR AB VAS OR TI Total nasal symptom severity OR AB Total nasal symptom severity OR TI TNSS OR AB TNSS OR TI Sinonasal outcome test-22 OR AB Sinonasal outcome test-22OR

TI SNOT-22 OR AB SNOT-22 OR TI Rhinosinusitis Outcome Measure-31 OR AB Rhinosinusitis Outcome Measure-31 OR TI RSOM-31 OR AB RSOM-31 OR TI 36-Item Short Form OR AB 36-Item Short Form OR TI SF-36 OR AB SF-36 OR TI Peak nasal inspiratory flow OR AB Peak nasal inspiratory flow OR TI University of Pennsylvania Small Identification Test OR AB University of Pennsylvania Small Identification Test OR TI UPSIT OR AB UPSIT

Sinusitis/syn OR Sinusitis/exp OR Sinus*:ti,ab OR "Chronic rhinosinusitis":ti,ab OR CRS:ti,ab OR CRSsNP:ti,ab OR "Nose polyp"/syn OR "Nose polyp"/exp OR "Nose polyp*":ti,ab OR "Nasal polyp*":ti,ab OR Papillom*:ti,ab Polyp/syn OR Polyp/exp OR Polyp*:ti,ab

AND

Immunotherapy/syn OR Immunotherapy/exp OR Immun*:ti,ab OR Therap*:ti,ab OR Immunomodulation/syn OR Immunomodulation/exp OR Immunomodulat*:ti,ab OR "Monoclonal antibody"/syn OR "Monoclonal antibody"/exp OR "Monoclonal antibod*":ti,ab OR

Antibody/syn OR Antibody/exp OR Antibod*:ti,ab OR Immunoglobulin/syn OR Immunoglobulin/exp OR

Cytokine/syn OR Cytokine/exp OR Cytokine*:ti,ab
OR Interleukin*:ti,ab OR IL-5:ti,ab OR IL-4:ti,ab
OR IL-13:ti,ab OR Interferon/syn OR Interferon/exp
OR Interferon*:ti,ab OR Omalizumab/syn OR Omalizumab/exp OR Omalizumab:ti,ab OR Xolair:ti,ab OR Immunoglobulin E/syn OR Immunoglobulin E/exp OR Immunoglobulin E:ti,ab OR IgE:ti,ab OR "Immunoglobulin E antibody"/syn OR "Immunoglobulin E antibody"/exp OR Anti-IgE:ti,ab OR Mepolizumab/syn OR Mepolizumab/exp OR Mepolizumab:ti,ab OR Reslizumab/syn OR Reslizumab/exp OR Reslizumab:ti,ab OR Benralizumab/syn OR Benralizumab/exp OR Benralizumab:ti,ab OR

AMG 282:ti,ab OR Sialic acid/syn OR Sialic acid/exp OR Sialic acid:ti,ab

AND

"Quality of life"/syn OR "Quality of life"/exp OR "Quality of life":ti,ab OR "Quality-of-life":ti,ab OR "Health-related-quality-of-life":ti,ab OR "Life quality":ti,ab OR QOL:ti,ab OR HRQOL:ti,ab OR Morbidity/syn OR Morbidity/exp OR Morbidity*:ti,ab OR "Lund-Mackay":ti,ab OR "Polyp size":ti,ab OR "Visual analogue scale"/syn OR "Visual analogue scale"/exp OR "Visual analogue scale":ti,ab OR VAS:ti,ab OR "Total nasal symptom severity":ti,ab OR TNSS:ti,ab OR "Sinonasal outcome test-22":ti,ab OR SNOT-22:ti,ab OR "Rhinos-

inusitis Outcome Measure-31":ti,ab OR RSOM-31:ti,ab OR "36-Item Short Form":ti,ab OR SF-36:ti,ab OR "Peak nasal inspiratory flow":ti,ab OR "University of Pennsylvania Small Identification Test":ti,ab OR UPSIT:ti,ab

Cochrane Database of Systematic Reviews Embase

Sinus* OR Chronic rhinosinusitis OR CRS OR CRSsNP OR Nose polyp* OR Nasal polyp* OR

Papillom* OR Polyp*

AND

Immun* OR Therap* OR Immunomodulat* OR Monoclon* OR Antibod* OR Interleukin* OR Cytokine* OR IL-5 OR IL-4 OR IL-13 OR Interferon* OR Omalizumab OR Xolair OR IgE Anti-IgE OR Mepolizumab OR Reslizumab OR Benralizumab OR AMG 282 OR Sialic acid

AND

Quality of life OR Quality-of-life OR Health-related-quality-of-life OR Life quality OR QOL OR

HRQOL OR Morbidity* OR Lund-Mackay OR Polyp size* OR Visual analog scale* OR VAS OR

Total nasal symptom severity OR TNSS OR Sinonasal outcome test-22 OR SNOT-22 OR Rhinosinusitis Outcome Measure-31 OR RSOM-31 OR 36-Item Short Form OR SF-36 OR Peak nasal inspiratory flow OR University of Pennsylvania Small Identification Test OR UPSIT