

Anti-IgE and Anti-IL5 Biologic Therapy in the Treatment of Nasal Polyposis: A Systematic Review and Meta-analysis

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Alexander Rivero, MD¹, and Jonathan Liang, MD, FARS¹

Abstract

Objective: To determine the role of biologic therapy on sinonasal symptoms and objective outcomes in chronic rhinosinusitis with nasal polyposis (CRSwNP).

Methods: PubMed, OVID MEDLINE, and Cochrane Central were reviewed from 2000 to 2015. Inclusion criteria included English-language studies containing original data on biologic therapy in CRSwNP patients with reported outcome measures. Two investigators independently reviewed all manuscripts and performed quality assessment and quantitative meta-analysis using validated tools.

Results: Of 495 abstracts identified, 7 studies fulfilled eligibility: 4 randomized control trials (RCT), 1 case-control, and 2 case series. Outcome measures included nasal polyp score (NPS), computer tomography score (5), and symptom scores (5). Meta-analysis was performed on 5 studies: Anti-IL5 therapy (mepolizumab/reslizumab) and anti-IgE therapy (omalizumab) demonstrated a standard mean difference of NPS improvement of -0.66 (95% CI, -1.24 to -0.08) and -0.75 (95% CI, -1.93 to 0.44), respectively, between biologic therapy and placebo. Quality assessment indicated a low to moderate risk of bias for the RCTs.

Conclusion: Biologic therapies may prove beneficial in the treatment of recalcitrant nasal polyposis in select populations. In meta-analysis, anti-IL5 therapy demonstrates a reduction in nasal polyp score. Anti-IgE therapy reduces nasal polyp score in patients with severe comorbid asthma. Additional high-level evidence is needed to assess clinical efficacy.

Keywords

nasal polyposis, anti-IgE, anti-IL5, biologics, systematic review, omalizumab, mepolizumab, reslizumab

Introduction

Chronic rhinosinusitis (CRS) is defined as objective mucosal inflammation of nose and paranasal sinuses lasting longer than 3 months without complete symptom resolution.^{1,2} This disease entity comes in several different etiologies, including CRS with (CRSwNP) and without nasal polyps (CRSsNP). The initial treatment of CRS is medical management, and adjunctive surgical intervention is considered for those that fail to respond adequately to medical therapy. Routine medical management for CRS usually includes nasal saline irrigations and intranasal steroids for maintenance therapy and systemic corticosteroids and antibiotics for exacerbations.¹⁻³ In patients with CRSwNP who fail medical management, endoscopic sinus surgery may be considered to relieve obstruction, remove inflammatory tissue, and improve local delivery of topical therapies. Recalcitrant cases of CRSwNP may require multiple surgical interventions and additional adjuvant medical therapy.^{2,4} Adjuvant medical therapy that has been employed for

recalcitrant CRSwNP include leukotriene antagonists, low-dose macrolides, oral antifungals, topical antibiotics, and biologic agents.²

Several studies have implicated distinct inflammatory pathways in CRS. Specifically, in CRSwNP, an upregulation of the T_H2 system with predominantly eosinophilic inflammation and elevated levels of IL-5 and IgE exists for Caucasian patients.⁵⁻⁸ It is postulated that the release of toxic products by eosinophils leads to further inflammation and subsequent polyp formation. Furthermore, upregulation of cytokines such as IL-5 serve to encourage migration of eosinophils to these locations and propagate the inflammatory response.⁸ In non-Caucasian patients, Cao et al⁹ found that

¹Kaiser Permanente, Oakland, California, USA

Corresponding Author:

Alexander Rivero, MD, Kaiser Permanente, 3600 Broadway, Oakland, CA 94611, USA.

Email: Alexander.rivero@kp.org

there was less expression of IL-5 and eotaxin and less eosinophils present in the setting of similar nasal polyps.⁸ These similar processes of inflammation have been noted in the functional units of the lung forming the basis of the unified airway theory.¹⁰⁻¹³ Further evidence of the unified airway is noted in the vast literature noting the association between asthma and CRS.¹⁴⁻¹⁹ A large majority of patients with asthma demonstrate abnormal CT sinus findings, and there is a high correlation between asthma severity and CT sinus disease.^{11,15,20} Furthermore, treatment of CRS with either medical management or functional endoscopic sinus surgery has led to decreases in asthma-related medication use, asthma exacerbations, and associated hospitalizations.²¹⁻²⁴ Conversely, treatment of asthma with omalizumab has been linked with decreases in prescription antibiotic administration.¹⁹ Given these correlations, biologic agents such as anti-IgE antibodies (omalizumab) and anti-IL5 antibodies (mepolizumab, reslizumab), currently FDA approved for the management of asthma, provide a potential therapeutic target for the management of CRSwNP in select patients.

The impetus to develop new efficacious treatment for CRSwNP and the pathophysiologic implications offered by the unified airway theory lead us to hypothesize that biologic therapies may help improve clinical outcomes in patients with recalcitrant CRSwNP. Anti-IgE agents (omalizumab) and anti-IL5 agents (reslizumab, mepolizumab) may demonstrate benefit not just in asthma and allergic rhinitis. The purpose of this study is to systematically review the literature to determine the efficacy of biologic therapy on sinonasal symptoms and objective clinical outcomes in recalcitrant CRSwNP.

Methods

Search Strategy

A systematic review using PubMed, OVID MEDLINE, and Cochrane Central databases was conducted for biologic therapy in treatment of CRSwNP from January 1, 2000, to December 31, 2015. Search criteria terms using medical subject heading (MeSH) terms included *chronic rhinosinusitis*, *nasal polyps*, *biologics*, *anti-IgE*, *anti-IL5*, *omalizumab*, *reslizumab*, and *mepolizumab*. After initial query with the aforementioned search terms, articles were then filtered for full text availability, human subject research, and English language, and subsequent abstracts were reviewed for selection. Further selection of studies was obtained from bibliography searches of selected articles. This systematic review qualified as non-human subject research and thus was exempt from approval by the institutional review board.

Selection Criteria

All English-language, human studies with original data on biologic therapy in CRSwNP were included. Nonhuman,

radiological, anatomical, and histological studies were excluded. Articles with unobtainable full text, review articles, case reports, biologic agents used for treatment in other conditions, and studies without outcome measures were further excluded. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines were followed for the selection and review of articles.

Data Extraction

Measures extracted included: nasal polyp score (NPS), computed tomography (CT) score, and symptom score. Two independent reviewers were involved in the full-text review. Only articles in which individual data could be extracted were selected for review.

Quality Assessment

Validated bias tools including the Cochrane Risk of Bias (CRB) tool and the Newcastle-Ottawa Quality Assessment (NOQA) scale were used for assessment of quality of evidence. The CRB tool covers 6 domains of bias: selection bias, performance bias, detection bias, attrition bias, reporting bias, and other bias. Studies are graded as low, moderate, or high risk of bias based on these domains.²⁵ The NOQA scale was used for assessment of case-control and case series studies. For case series, questions regarding control group were rated as not applicable (N/A). The maximum possible total score for a case control study is 10 stars, and maximum possible total score for a case series is 4 stars.²⁶

Statistical Analysis/Meta-analysis

The primary outcome of interest was nasal polyp score. The secondary outcome measures included CT score and symptom scores. Analysis compared biologic therapy versus placebo in the placebo-controlled randomized controlled trials (RCTs). Data from uncontrolled studies were summarized with respect to each outcome measure of interest.

Meta-analysis of outcomes with a continuous measure (comparison of means and standard deviations between control and treatment groups) was performed with Review Manager (RevMan) software (The Nordic Cochrane Centre, Copenhagen). Given the likelihood of study variability, a random effects model was used, the standardized mean difference (SMD) and 95% confidence interval (CI) was calculated, and Forest plots were generated. The SMD represents a transformation of the study outcome data into standard deviation units by dividing the difference in mean outcome between 2 groups by the pooled standard deviation. Negative values indicated improvement, and positive values indicated worsening of the measure of interest. Heterogeneity was assessed with the I^2 statistic; the values of 25%, 50%, and 75% were considered to indicate low,

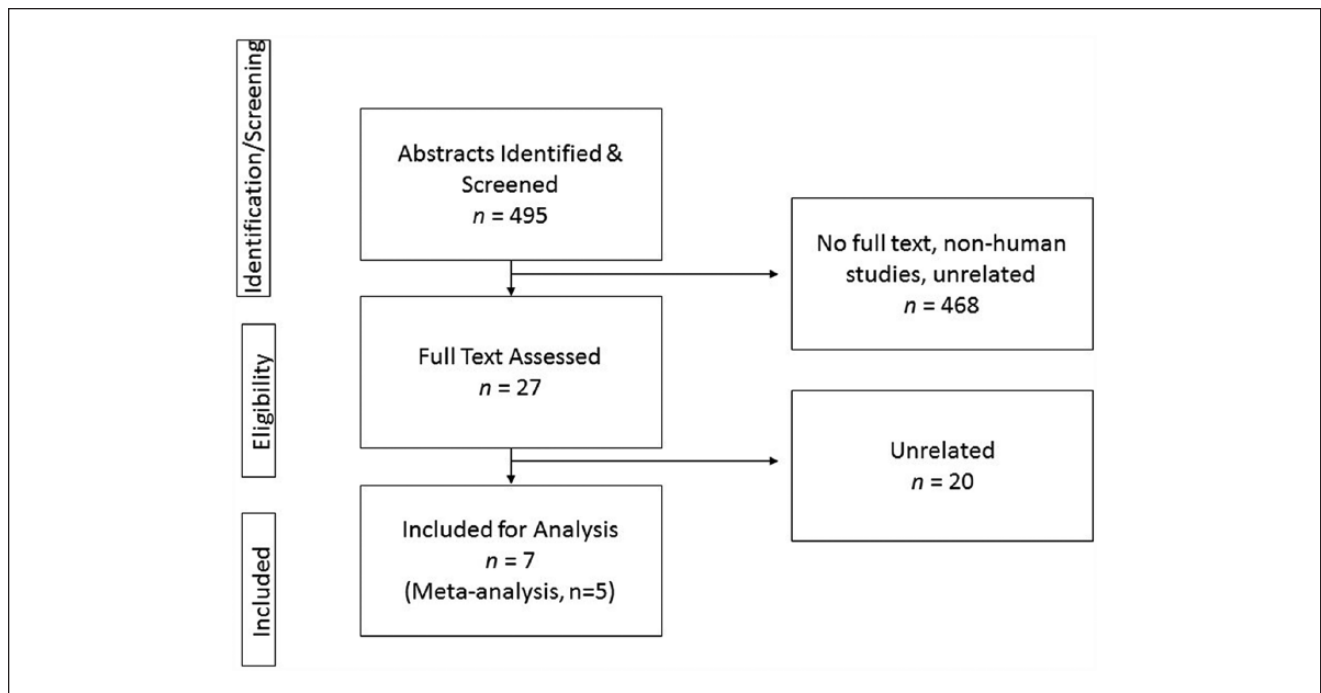


Figure 1. Search strategy.

medium, and high heterogeneity, respectively. Post hoc meta-analysis was then performed on the subset of patients with severe comorbid asthma.

Results

A total of 495 abstracts resulted from our initial query. After selection and review as illustrated in Figure 1, seven studies fulfilled eligibility. There were four RCTs, one case-control study, and two case series (Table 1). Outcome measures included NPS, CT score, and symptom scores.

We included 4 RCTs, which included a total of 92 patients and had follow-up between 15 weeks and 12 months (mean follow-up of 8 months).^{8,13,27,28} Of the RCTs, two investigated anti-IgE therapy, and two investigated anti-IL5 therapy. All studies focused on three medications: omalizumab (anti-IgE), reslizumab (anti-IL5), and mepolizumab (anti-IL5). The single case-control study had a total of 8 patients (4 controls, 4 treatment group) and follow-up of 10.5 months.²⁹ The two case series had a total of 25 patients and follow-up of 16 weeks and 28 months.^{30,31}

Nasal Polyp Score

The primary outcome of interest, measured in 6 of the 7 studies, was NPS.^{8,13,27-29,31} All six studies (100%) demonstrated improvement in NPS. Nasal polyp score was measured as total polyp score (TPS) in 4 of 6 studies.^{8,27,28,31} One study used a 3-grade endoscopic nasal polyp grade.²⁹

Another study used a 4-point endoscopic nasal polyp grade similar to TPS but not as formally defined.¹³ Total polyp score is defined as a grade of 1 to 4 representing the summation of both nares: grade 0 being no polyps, grade 1 being small polyps in the middle meatus not reaching below the inferior border of the middle turbinate, grade 2 being polyps reaching below the lower border of the middle turbinate, grade 3 being large polyps reaching the lower border of the inferior turbinate or polyps medial to the middle concha, and grade 4 being large polyps causing complete obstruction of the inferior meatus.

CT Score

Five studies included CT score.^{8,13,28-30} Four of five (80%) studies demonstrated improvement in CT score. The CT score was described as Lund-Mackay score³² in three studies,²⁸⁻³⁰ percent opacification in one study,¹³ and percent improvement in one study.⁸ Studies that included this measure reported low interrater variability.

Symptom Score

Five studies included measures of clinical symptoms, including quality of life measures.^{8,13,27,28,30} These scores were grouped broadly as “symptom scores” but included University of Pennsylvania Smell Identification Test (UPSIT) scores,¹³ Sinonasal Outcome Test 20 (SNOT-20),^{13,30} 36-Item Short Form Survey (SF-36),^{13,28} Asthma Quality of Life

Table 1. Summary of Included Articles.

Lead Author, Year	LOE	Therapy	Sinonasal Disease	Asthma	Treatment Group	Control Group	Outcomes	Conclusions
Gevaert, 2006 ²⁷	Ib	Reslizumab (anti-IL5)	Severe polyposis or recurrent after surgery	5/8 in 3 mg/kg arm, 7/8 in 1 mg/kg arm, 6/8 control asthma hx	n = 8 at 3 mg/kg; n = 8 at 1 mg/kg	n = 8, placebo	Sx, NPS (TPS)	1 mg/kg arm had more responders improving NPS No significant change in CT score
Gevaert, 2011 ⁸	Ib	Mepolizumab (anti-IL5)	Severe polyposis or recurrent after surgery	10/20 Tx and 3/10 control asthma hx	n = 20 at 750 mg	n = 10, placebo	Sx, NPS (TPS), CT (% improvement)	Significant improvement in all 3 outcomes
Pinto, 2010 ¹³	Ib	Omaliuzumab (anti-IgE)	Severe polyposis and recurrent after surgery	5/7 tx and 3/7 control asthma inhaler use reported	n = 7 at 0.016 mg/kg per IU total serum IgE/mL	n = 7 placebo	Sx (UPSIT, SNOT-20, SF-36), NPS (endoscopic polyp grade, 4 pt), CT (% opacification)	Significant improvement in CT score No significant improvement in Sx or NPS
Gevaert, 2013 ²⁸	Ib	Omaliuzumab (anti-IgE)	CRSwNP and asthma	All patients with comorbid asthma	n = 16 wt and IgE based dose (max 350 mg)	n = 8, placebo	Sx (SF-36), NPS (TPS), CT (Lund-Mackay)	Significant improvement in all outcomes
Penn, 2007 ²⁹	3b	Omaliuzumab (anti-IgE)	CRSwNP after surgery and asthma	All patients with atopic asthma	n = 4 (150-375 mg)	n = 4, Historically matched controls	NPS (endoscopic polyp grade), CT (Lund-Mackay)	Significant improvement in NPS No significant improvement in CT score
Vennera, 2011 ³¹	4	Omaliuzumab (anti-IgE)	Asthma with CRSwNP	All patients with severe asthma	n = 19, wt and IgE based dose	n/a	NPS (TPS)	Significant decrease in NPS and also intranasal steroid use
Tajiri, 2013 ³⁰	4	Omaliuzumab (anti-IgE)	ECRS with asthma	All patients with severe atopic asthma	n = 6	n/a	Sx (SNOT-20, AQLQ), CT (Lund-Mackay)	Significant decrease in Sx and CT scores

Abbreviations: AQLQ, Asthma Quality of Life Questionnaire; CRSwNP, chronic rhinosinusitis with nasal polyposis; CT, computed tomography; ECRS, eosinophilic chronic rhinosinusitis; NPS, nasal polyp score; RCT, randomized controlled trial; SF-36, 36-Item Short Form Survey; SNOT-20, Sinonasal Outcome Test 20; Sx, symptoms; TPS, total polyp score; UPSIT, University of Pennsylvania Smell Identification Test.

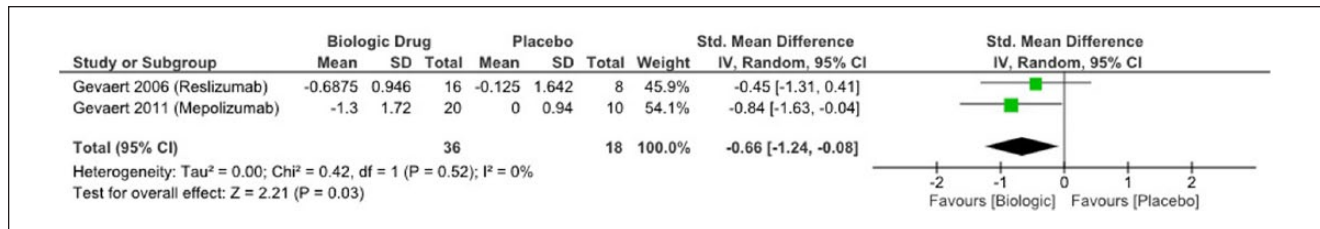


Figure 2. Standard mean difference of nasal polyp score—anti-IL5 therapy versus placebo forest plot.

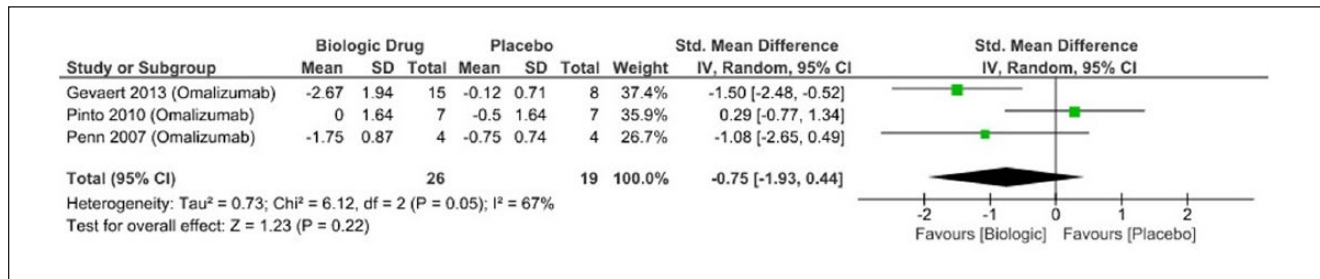


Figure 3. Standard mean difference nasal polyp score—anti-IgE therapy versus placebo forest plot.

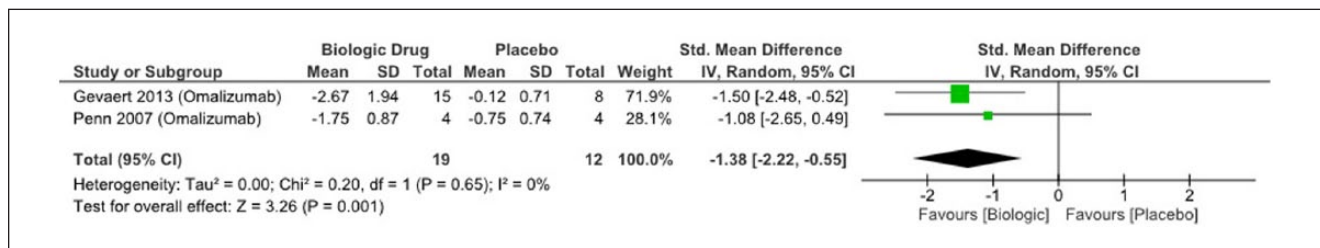


Figure 4. Standard mean difference nasal polyp score—anti-IgE + concomitant asthma versus placebo forest plot.

Questionnaire (AQLQ),³⁰ as well as other nonvalidated symptom-specific questions regarding nasal obstruction, loss of sense of smell, and presence of rhinorrhea.^{8,27} Of these, three studies (60%) demonstrated improvement in patient symptom scores.^{8,28,30}

Meta-analysis

Meta-analysis was performed on the five studies in NPS group in which individual data could be obtained, analyzed, and compared to placebo.^{8,13,27-29} The SMD of NPS improvement for anti-IL5 therapy (mepolizumab, reslizumab) was -0.66 (95% CI, -1.24 to -0.08) between biologic therapy and placebo; there was a low level of heterogeneity in the compared data ($I^2 = 0\%$) (Figure 2). The SMD of NPS improvement for anti-IgE therapy (omalizumab) therapy was -0.75 (95% CI, -1.93 to 0.44); there was a moderate level of heterogeneity in the compared data ($I^2 = 67\%$) (Figure 3). Post hoc analysis of only studies in which patients had concomitant severe asthma were included (in

these cases, only anti-IgE therapy was used), the SMD between placebo and omalizumab is -1.38 (95% CI, -2.22 to -0.55), and there was a low level of heterogeneity in the compared data ($I^2 = 0\%$) (Figure 4).^{28,29}

Quality assessment

Using the Cochrane Risk of Bias tool, the overall quality assessment for the RCTs indicated a low to moderate risk of bias (Table 2). Most risk of bias in the RCTs was noted in the incomplete outcome reporting in three studies and blinding of participants in one study. Using the NOQA scale, quality assessment on the non-RCT studies demonstrated 8 out of 10 stars and 2 out of 4 stars for the case-control studies and case series, respectively (Table 3).

Discussion

The etiology of CRS has yet to be clearly elucidated and thus continues to pose interesting treatment challenges.

Table 2. Quality Assessment of Level I Evidence Studies (Modified Cochrane Collaboration Tool for Assessing Risk of Bias).^a

Potential Source of Bias	Scoring	Study			
		Gevaert 2006	Gevaert 2011	Gevaert 2013	Pinto 2010
Was there random allocation of subjects?	Random = 0, nonrandom = 1	0	0	0	0
Was the allocation scheme concealed?	Concealed = 0, not concealed = 1	0	0	0	0
Were the interventions concealed from study personnel and participants?	Complete blinding = 0, incomplete blinding = 1	0	0	0	0
Were incomplete data adequately addressed?	Addressed = 0, not addressed = 1	1	1	0	1
Was there selective outcome reporting?	None = 0, yes = 1	0	0	0	0
Were there any other important sources of bias?	None = 0, yes = 1	1	1	1	0
Total score		2	2	1	1

^aInterpretation of score (minimum possible score is 0, maximum possible score is 6): 0 to 1 point indicates low risk of bias (least bias, best quality study with valid results), 2 to 3 points indicates medium risk of bias (susceptible to some bias but not enough to invalidate results), and 4 to 6 points indicates high risk of bias (most bias, worst quality study with significant flaws).

Table 3. Quality Assessment of Level 3 and 4 Evidence Studies (Newcastle-Ottawa Assessment Scale).^a

Author	Selection Grade (Maximum 4 Stars)	Comparability Grade (Maximum 2 Stars)	Exposure Grade (Maximum 4 Stars)	Total
Venerra 2002	*	N/A	*	**
Tajiri 2003	*	N/A	*	**
Penn 2007	***	**	***	*****

^aMaximum possible total score for case control study is 10 stars, and maximum possible total score for case series is 4 stars. N/A, for assessment of case series article, questions regarding control group are not applicable.

Recalcitrant CRS often encourages otolaryngologists, including rhinologists, to think out of the box and apply treatment options employed in other comorbid conditions with similar pathophysiology. The unified airway theory suggests that the upper airways, nose, paranasal sinuses, larynx, and trachea all the way down to the functional bronchioles function as a single unit that is subject to similar inflammatory insults.^{10,13,33} Patients who suffer from asthma frequently suffer from allergic rhinitis and/or chronic sinusitis.¹⁹ In fact, allergies have been implicated in the development of CRS in many patients, though the causal relationship is not yet fully understood.^{13,34,35} It is well appreciated that IgE plays a key inflammatory role in allergic rhinitis and asthma and has recently been implicated in the cascade of polyposis development in CRSwNP.¹¹⁻¹³ These findings have been further corroborated by the expression of elevated levels of IgE, IL5, and eosinophils in tissue samples of patients with CRSwNP.^{5,13,36,37} These findings implicate novel and potentially advantageous uses of anti-IgE and anti-IL5 monoclonal antibodies in the treatment of patients with recalcitrant CRSwNP. Our review

suggests that these therapies may prove beneficial in the treatment of CRSwNP in select populations. Of the included studies, the majority demonstrated improvement in NPS score (6 of 6, 100%), CT score (4 of 5, 80%) and symptom score (3 of 5, 60%). Moreover, our meta-analysis demonstrates statistically significant reduction in NPS with anti-IL5 therapy (mepolizumab, reslizumab) compared with placebo (−0.69; 95% CI, −1.24 to −0.12; $P = .02$). When the anti-IgE therapy studies were evaluated, there was not a statistically significant reduction in NPS compared with placebo (−0.75; 95% CI, −1.93 to 0.44; $P = .22$), though it trended toward improvement. Post hoc analysis of studies in which patients had concomitant severe asthma as formal inclusion criteria again found a statistically significant reduction in NPS (−1.38; 95% CI, −2.22 to −0.55; $P = 0.001$). The clinical significance of the absolute numerical value is difficult to ascertain but at minimum indicates a reduction in nasal polyp burden with anti-IL5 therapy and anti-IgE therapy in patients with severe comorbid asthma.

Over recent decades, it has become important to identify the different phenotypes of diseases affecting the unified

airway. For example, it has become clear that the once homogeneously treated asthma patient may not respond well to traditional treatment with inhaled corticosteroids. Phenotypic variants including the allergic and eosinophilic subtypes have become critical to distinguish in order to provide optimal treatment. It is well appreciated that reduction of sputum eosinophils has resulted in decreased asthma exacerbations and improved control.³⁷⁻³⁹ Inhibition of IL5, a pro-inflammatory cytokine involved in the maturation and recruitment of eosinophils, has also been shown to decrease sputum eosinophils in asthma patients.^{37,40} Anti-IL5 therapy has been demonstrated as effective in improving airway function and qualitative symptom scores when selecting for patients with eosinophilic asthma.³⁷ Specifically, mepolizumab and reslizumab have been FDA approved in late 2015 and early 2016, respectively, for the treatment of patients with severe asthma and concomitant eosinophilia and have demonstrated to reduce asthma exacerbations with minimal side effects.⁴¹ Similarly, omalizumab, FDA approved in 2003, has also been a key player in the management of chronic moderate to severe asthma, demonstrating reduction in asthma exacerbations with a narrow adverse event profile.⁴¹ A similar endotype-based therapy implication has been made regarding patients with CRSwNP. Several studies have found an increase in eosinophil count, tissue IgE, and IL5 in the polyps of Caucasian patients with CRSwNP.^{5,42} It follows that reducing eosinophilia and its associated inflammatory cascade could lead to decrease in nasal polyposis, especially in patients with concomitant asthma. Furthermore, the enterotoxins produced by *Staphylococcus aureus* have been implicated in the formation of polyclonal IgE and increased eosinophilic inflammation by acting as superantigens in nasal/polyp tissue.³⁶ Creation of the aforementioned IgE has also been strongly associated with asthma in patients with CRSwNP.⁴³ In 2013, Gevaert et al²⁸ reported their findings on the use of anti-IgE (omalizumab) in patients with CRSwNP with comorbid asthma finding a statistically significant decrease in the NPS, CT, and symptom scores. Not surprisingly, patients also reported a qualitative improvement in their asthma symptoms as measured by the validated Asthma Quality of Life Questionnaire (AQLQ). Interestingly, when the treatment arm was divided into allergic and nonallergic responders ($n = 7$ and $n = 8$, respectively) based on skin prick testing, the allergic group had an expected statistically significant improvement in CT score when compared to the nonallergic group, but the nonallergic group had a significant improvement in AQLQ score where the allergic group did not. In our meta-analysis, this study yielded the most definitive decrease in nasal polyp score when comparing treatment to placebo with a standard mean difference of -1.50 (95% CI, -2.48 to -0.52). In their retrospective case-control study, Penn and Mikula²⁹ looked at 4 patients with CRSwNP and concomitant asthma and also found decreases in NPS. Gevaert and

colleagues^{8,27} had also published data in 2006 and 2011 specifically relating to the safety and use of anti-IL5 treatment (mepolizumab, reslizumab) in patients with CRSwNP, most of whom failed endoscopic sinus surgery. These studies further corroborate the decrease in NPS in the treatment group and also demonstrate improvements in CT and symptom scores. Unfortunately, these conclusions were limited due to high dropout rate in 1 study⁸ and surgery in the treatment group in the other.²⁷

Adverse events

Safety of biologic therapies mepolizumab, reslizumab, and omalizumab has been established in prior studies in the setting of treatment of asthma.⁴¹ A common adverse event is hypersensitivity and anaphylaxis, and thus medications should be administered in a health care setting under the guidance of a trained health care professional. Reslizumab and omalizumab carry with them a theoretical increased risk of malignancy. However, there have been no clusters of malignancy type in the safety studies of these medications. Furthermore, follow-up studies of omalizumab have also failed to demonstrate a statistically significant increased risk of malignancy. Though causal relationships have not been demonstrated, eosinophilic vasculitis like conditions such as Churg-Strauss Syndrome have also been reported with omalizumab, usually with concomitant reduction of corticosteroid therapy. Lastly, opportunistic infection with herpes zoster and helminthic infections are theoretical risks, and monitoring for these infections should be undertaken at the discretion of the provider. Given these potential adverse events, the authors do not recommend administration of these medications as first-line treatment of CRSwNP.

Limitations

Only 7 total studies were found to meet inclusion criteria and included in the systematic review. Of these 7, only 4 were level 1b RCTs. The paucity of data on the subject is likely due to the difficulty of designing and carrying out well-performed RCTs. Meta-analysis was performed for the outcome of NPS in 5 studies. Nasal polyp score, our primary outcome measurement due to the relative consistency of this outcome in all the studies, was used as surrogate marker for disease burden and thus disease severity as perceived by the patient. However, studies have demonstrated that endoscopy score may not necessarily correlate with patient symptoms.⁴⁴ Limited and heterogeneous data for the other outcome variables of CT score and symptom score precluded quantitative analysis of these variables. Quality assessment demonstrated a low to moderate risk of bias for both RCT and non-RCT using our validated measurement scales. Pooling of data is inherently biased to the heterogeneity of the data used to perform meta-analysis.

Our meta-analysis yields low to moderate heterogeneity, with I^2 range of 0% to 67%.

Future Directions

Biologic therapy can provide new options for the medical management of recalcitrant CRSwNP. Additional RCTs on anti-IgE and anti-IL5 therapy designed specifically to investigate sinonasal outcomes will be valuable to understand the role of biologics in CRSwNP. The current level 1 evidence focuses on asthma outcomes, with sinonasal outcomes as secondary endpoints. At the time of the systematic review, only studies on omalizumab, mepolizumab, and reslizumab were available. A very recent RCT on dupilumab, a monoclonal antibody binding to IL4 and IL13 receptors, by Bachert et al⁴⁵ demonstrates reduced nasal polyp burden and Lund-Mackay scores and improved olfactory and quality of life questionnaire scores in patients with refractory CRSwNP. This study focused specifically on sinonasal outcomes and provides a model for future studies investigating biologics in recalcitrant CRSwNP. Dupilumab, recently FDA approved for atopic dermatitis, is considered a “breakthrough therapy.” If additional studies demonstrate continued efficacy, this would be a worthy addition to the current biologic armamentarium.

Conclusion

Advances in biologic therapy for T_H2 -mediated diseases such as asthma and allergic rhinitis has led to investigation of their use in CRSwNP. Biologic therapy may prove beneficial in the treatment of recalcitrant nasal polyposis in select populations. Our meta-analysis demonstrates that anti-IL5 therapy shows statistically significant reduction in NPS in CRSwNP patients, and anti-IgE therapy shows statistically significant reduction in NPS in CRSwNP patients with concomitant severe asthma. These early studies show promising results, but additional high-level evidence studies are needed to determine efficacy of biologic therapies in recalcitrant CRSwNP before widespread use can be justified. Currently, the use of biologic therapies should be reserved for select patients with recalcitrant CRSwNP and evidence of atopic or eosinophil-driven disease that has been unresponsive to other adjuvant medical therapies.

Authors' Note

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Declaration of Conflicting Interests

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References

1. Piromchai P, Kasemsiri P, Laohasiriwong S, Thanaviratnanich S. Chronic rhinosinusitis and emerging treatment options. *Int J Gen Med*. 2013;6:453-464.
2. Rosenfeld RM, Piccirillo JF, Chandrasekhar SS, et al. Clinical practice guideline (update): adult sinusitis. *Otolaryngol Head Neck Surg*. 2015;152(2 suppl):S1-S39.
3. Rudmik L, Soler ZM. Medical therapies for adult chronic sinusitis: a systematic review. *JAMA*. 2015;314(9):926-939.
4. Fandiño CM, Macdonald KI, Lee J, Witterick IJ. The use of postoperative topical corticosteroids in chronic rhinosinusitis with nasal polyps: a systematic review and meta-analysis. *Am J Rhinol Allergy*. 2013;27(5):e146-e157.
5. Bachert C, Gevaert P, Holtappels G, Johansson SGO, Cauwenberge P. Total and specific IgE in nasal polyps is related to local eosinophilic inflammation. *J Allergy Clin Immunol*. 2001;107(4):607-614.
6. Riechelmann H, Deutschle T, Rozsasi A, Keck T, Polzehl D, Bürner H. Nasal biomarker profiles in acute and chronic rhinosinusitis. *Clin Exp Allergy*. 2005;35(9):1186-1191.
7. Stevens WW, Schleimer RP, Chandra RK, Peters AT. Biology of nasal polyposis. *J Allergy Clin Immunol*. 2014;133(5):1503-1503.e4.
8. Gevaert P, Van Bruaene N, Cattaert T, et al. Mepolizumab, a humanized anti-IL-5 mAb, as a treatment option for severe nasal polyposis. *J Allergy Clin Immunol*. 2011;128(5):989-995.
9. Cao P-P, Li H-B, Wang B-F, et al. Distinct immunopathologic characteristics of various types of chronic rhinosinusitis in adult Chinese. *J Allergy Clin Immunol*. 2009;124(3):478-484.
10. Krouse JH, Brown RW, Fineman SM, et al. Asthma and the unified airway. *Otolaryngol Head Neck Surg*. 2007;136(5 suppl):S75-S106.
11. Baroody FM, Suh SH, Naclerio RM. Total IgE serum levels correlate with sinus mucosal thickness on computerized tomography scans. *J Allergy Clin Immunol*. 1997;100(4):563-568.
12. Naclerio RM, Baroody FM, Pinto JM. Should clinicians use omalizumab for the treatment of nasal polyps? *J Allergy Clin Immunol*. 2013;132(1):247.
13. Pinto JM. A randomized, double-blind, placebo-controlled trial of anti-IgE for chronic rhinosinusitis. *Rhinol J*. 2010;48(3):318-324.
14. Lin DC, Chandra RK, Tan BK, et al. Association between severity of asthma and degree of chronic rhinosinusitis. *Am J Rhinol Allergy*. 2011;25(4):205-208.
15. Bresciani M, Paradis L, Des Roches A, et al. Rhinosinusitis in severe asthma. *J Allergy Clin Immunol*. 2001;107(1):73-80.
16. Matsuno O, Ono E, Takenaka R, et al. Asthma and sinusitis: association and implication. *Int Arch Allergy Immunol*. 2008;147(1):52-58.

17. Jarvis D, Newson R, Lotvall J, et al. Asthma in adults and its association with chronic rhinosinusitis: the GA2LEN survey in Europe. *Allergy*. 2012;67(1):91-98.
18. Alkire BC, Bhattacharyya N. An assessment of sinonasal anatomic variants potentially associated with recurrent acute rhinosinusitis. *Laryngoscope*. 2010;120(3):631-634.
19. Chandra RK, Clavenna M, Samuelson M, Tanner SB, Turner JH. Impact of omalizumab therapy on medication requirements for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2016;6(5):472-477.
20. ten Brinke A, Grootendorst DC, Schmidt JT, et al. Chronic sinusitis in severe asthma is related to sputum eosinophilia. *J Allergy Clin Immunol*. 2002;109(4):621-626.
21. Vashishta R, Soler ZM, Nguyen SA, Schlosser RJ. A systematic review and meta-analysis of asthma outcomes following endoscopic sinus surgery for chronic rhinosinusitis. *Int Forum Allergy Rhinol*. 2013;3(10):788-794.
22. Ikeda K, Tamura G, Shimomura A, et al. Endoscopic sinus surgery improves pulmonary function in patients with asthma associated with chronic sinusitis. *Ann Otol Rhinol Laryngol*. 1999;108(4):355-359.
23. Ragab S, Scadding GK, Lund VJ, Saleh H. Treatment of chronic rhinosinusitis and its effects on asthma. *Eur Respir J*. 2006;28(1):68-74.
24. Palmer JN, Conley DB, Dong RG, Ditto AM, Yarnold PR, Kern RC. Efficacy of endoscopic sinus surgery in the management of patients with asthma and chronic sinusitis. *Am J Rhinol*. 2001;15(1):49-53.
25. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *The BMJ*. 2011;343:d5928.
26. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. *Eur J Epidemiol*. 2010;25(9):603-605.
27. Gevaert P, Langlois D, Lackner A, et al. Nasal IL-5 levels determine the response to anti-IL-5 treatment in patients with nasal polyps. *J Allergy Clin Immunol*. 2006;118(5):1133-1141.
28. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110-116.
29. Penn R, Mikula S. The role of anti-IgE immunoglobulin therapy in nasal polyposis: a pilot study. *Am J Rhinol*. 2007;21(4):428-432.
30. Tajiri T, Matsumoto H, Hiraumi H, et al. Efficacy of omalizumab in eosinophilic chronic rhinosinusitis patients with asthma. *Ann Allergy Asthma Immunol*. 2013;110(5):387-388.
31. Vennera MDC, Picado C, Mullol J, Alobid I, Bernal-Sprekelsen M. Efficacy of omalizumab in the treatment of nasal polyps. *Thorax*. 2011;66(9):824-825.
32. Hopkins C, Browne JP, Slack R, Lund V, Brown P. The Lund-Mackay staging system for chronic rhinosinusitis: how is it used and what does it predict? *Otolaryngol Head Neck Surg*. 2007;137(4):555-561.
33. The unified airway: do we fully appreciate its impact in otolaryngology? *ENTtoday*. <http://www.enttoday.org/article/the-unified-airway-do-we-fully-appreciate-its-impact-in-otolaryngology/>. Accessed May 8, 2016.
34. Benninger MS. Rhinitis, sinusitis, and their relationships to allergies. *Am J Rhinol*. 1992;6(2):37-43.
35. Rachelefsky GS, Katz RM, Siegel SC. Chronic sinus disease with associated reactive airway disease in children. *Pediatrics*. 1984;73(4):526-529.
36. Bachert C, Zhang N, Patou J, van Zele T, Gevaert P. Role of staphylococcal superantigens in upper airway disease. *Curr Opin Allergy Clin Immunol*. 2008;8(1):34-38.
37. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184(10):1125-1132.
38. Groot JC, Brinke A, Bel EHD. Management of the patient with eosinophilic asthma: a new era begins. *ERJ Open Res*. 2015;1(1):00024-02015.
39. Green RH, Brightling CE, McKenna S, et al. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet Lond Engl*. 2002;360(9347):1715-1721.
40. Leckie MJ, ten Brinke A, Khan J, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet Lond Engl*. 2000;356(9248):2144-2148.
41. Fajt ML, Wenzel SE. Asthma phenotypes and the use of biologic medications in asthma and allergic disease: the next steps toward personalized care. *J Allergy Clin Immunol*. 2015;135(2):299-310.
42. Mygind N, Dahl R, Bachert C. Nasal polyposis, eosinophil dominated inflammation, and allergy. *Thorax*. 2000;55(suppl 2):S79-S83.
43. Zhang N, Gevaert P, van Zele T, et al. An update on the impact of *Staphylococcus aureus* enterotoxins in chronic sinusitis with nasal polyposis. *Rhinology*. 2005;43(3):162-168.
44. Pokharel M, Karki S, Shrestha BL, Shrestha I, Amatya RCM. Correlations between symptoms, nasal endoscopy computed tomography and surgical findings in patients with chronic rhinosinusitis. *Kathmandu Univ Med J KUMJ*. 2013;11(43):201-205.
45. Bachert C, Mannent L, Naclerio RM, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA*. 2016;315(5):469-479.