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Review Article

Immunomodulators in chronic rhinosinusitis

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Abstract *Objective:* To provide new insight into how chronic rhinosinusitis (CRS) is conceptualized and treated with a focus on immunomodulator therapy.
Data sources: Pubmed, Medline, and Embase.
Methods: A current review of the evidence is provided for immunomodulators investigated for treatment of CRS with nasal polyps (CRSwNP).
Results: Biologic therapies targeting IgE, IL-4, IL-5, and IL-13 for the treatment of CRSwNP have shown promise and are currently in phase 3 trials. Anti-immunoglobin E (IgE) therapy with omalizumab was assessed in 6 studies, anti-interleukin (IL)-5 therapy in 3 studies (2 mepolizumab, 1 reslizumab) and anti IL-4/IL-13 (dupilumab) therapy in one study. Studied outcomes varied, but the majority of trials identified clinical benefit of therapy over placebo. Other potential targets include thymic stromal lymphopoetin (TSLP), IL-25, IL-33, and sialic acid-binding immunoglobulin-type lectin (Siglec)-8. Small molecule drugs that target the dysregulation of the immune system in CRS are also being investigated for their immunomodulatory effects on inflammation.
Conclusion: Immunomodulator therapies for CRS currently in development will likely provide another therapeutic option for patients who have severe disease unresponsive to corticosteroids and surgery. Targeted monoclonal antibody therapies have shown encouraging results and phase 3 trials are underway. IL-4/IL-13 inhibition has shown the most promise to date. Further larger, well-designed trials are needed to improve understanding of these molecules and to offer endotype-driven therapies in the management of CRS. None of these therapeutics have shown long-term immunomodulation when discontinued and therefore further investigation into the pathomechanism of disease continues to be needed.

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Introduction

We live in an era of rapid advances in biomolecular and genetic engineering, which coupled with a better understanding of the pathologic mechanisms behind chronic inflammation, has allowed us to move toward more precise and personalized care. A vast array of potential immunologic targets have been discovered in recent years for the treatment of chronic diseases such as asthma, atopic dermatitis, and now potentially the contemporary management of chronic rhinosinusitis (CRS). Our understanding of the complexity of CRS continues to evolve and with it, better targeted immunomodulator therapies. CRS is prevalent and debilitating, affecting 12% of the United States population, up to 10% in China, and 11% in Europe.[1–3] The movement from describing CRS phenotype (polyps *vs* no polyps) to disease endotype is still in its infancy. The endotype describes the "pathomechanism" which allows for differentiation of disease subtypes at a functional and pathologic level based on molecular and cellular characteristics.[4] Understanding the differences in, for example, T-helper cell populations, cytokine composition, and downstream effectors can help to delineate these endotypes and hopefully lead to more effective, precise therapy. The recent application of biologic therapies that modulate immune effectors in eosinophilic CRS show promising results and are currently changing the way CRS therapy is conceptualized.

Currently CRS is divided into two subtypes, with nasal polyposis (CRSwNP) and without nasal polyposis (CRSsP). CRSwNP has a 20%—60% association with comorbid asthma and has a poorer prognosis with recurrence rates of 38—60% at 12 months.[5–8] In Western Caucasian patients, there is a Th2 inflammatory response with production of IL-4, IL-5, and IL-13 with corresponding predominance of eosinophilia, mast cells, and basophils while in Asian CRSwNP, neutrophilic predominance has been observed with Th1, Th17, or Th22 inflammatory responses.[9] IL-4 and IL-13 play a role in IgE isotype switching and upregulate sIgE receptors on eosinophils, mast cells, monocytes and basophils. IL-4 is also responsible for inflammatory cell chemotaxis with upregulation of vascular cell adhesion molecule-1 (VCAM-1). IL-5 plays a role in maturation, differentiation and activation of eosinophils and IL-5 and IL-13 are also involved in the innate immune epithelial responses. The Th-2 inflammatory response in CRSwNP is further amplified by the epithelial cell-activated type 2 innate lymphoid cells (ILC2s). These cells are early responders within the sinonasal mucosal and are activated by local epithelial factors (thymic stromal lymphopoietin (TSLP), IL-33 and IL-25).[10–12]

Other subtypes of CRS include allergic fungal rhinosinusitis (AFRS) and aspirin exacerbated respiratory disease (AERD). AFRS is characterized by an IgE-mediated hypersensitivity to fungus and presents with variable severity, from unilateral disease to pan-sinus involvement with fungal debris, polyps and eosinophilic mucin.[13] It appears that serum-specific IgE levels have been shown to correlate with disease severity.[14] The pathogenesis of AFRS is incompletely understood, but a local epithelial response triggered by fungus, and possibly *Staphylococcus aureus*, is believed to induce Il-33 activation of the Th-2 immune response.[15] Another subtype of CRSwNP, AERD presents with respiratory exacerbation in association with cyclooxygenase (COX)-1 inhibition.[16] Formerly known as Samter's triad, AERD patients exhibit nasal polyposis, bronchial asthma and inflammation in response to nonsteroidal anti-inflammatory drugs. AERD is considered a more severe subtype of CRS and affects 9.7% of CRSwNP patients.[17] Polymorphisms in the COX enzyme function result in increased production of cysteinyl leukotrienes, proinflammatory mediators that cause bronchoconstriction, eosinophilic inflammation, increased vascular permeability and mucus hypersecretion.[18,19]

Current treatment of CRS compared to other chronic inflammatory disorders lags in therapeutic options. The mainstay continues to be topical and oral steroids especially in eosinophilic CRSwNP, and often surgery when medical therapies are ineffective. Approximately 45,000 endoscopic sinus surgeries are performed annually in the United States but many patients continue to have recurrence of symptoms and disease with inadequate control.[20] Asthma and CRSwNP frequently coexist and share a similar Th2-type pattern especially in the Western world. As a result biologics developed for asthma are being investigated for treatment of CRS and could offer another therapeutic option for those patients with difficult to control disease. This article reviews the evidence for these immunomodulatory therapies and provides insight into how they may fit into the current paradigm for modern CRS therapy.

Anti-IgE monoclonal antibody therapy

Targeting IgE in CRSwNP seems logical considering the important role that IgE plays in similar Th2-type processes such as asthma and allergic rhinitis.[21] Serum levels of IgE have been shown to correlate with the severity of mucosal disease and is often seen correlated with aeroallergen sensitization or other microbialantigens.[22,23] Omalizumab (Xolair) was approved in 2003 for the treatment of moderate to severe persistent asthma not controlled by inhaled corticosteroids and is a human anti-IgE monoclonal antibody that binds free circulating IgE molecules, inhibiting its interaction with receptors on mast cells and basophils. The resulting effect is a reduction in allergen-induced cell degranulation and release of inflammatory mediators. Several studies have investigated its use in CRSwNP and comorbid asthma (Table 1). Of the six studies, there were two randomized double-blind placebo-controlled (RDBPC)

Table 1 Summary of published clinical trials using Omalizumab.

Author, year	Study design	Population	Treatment groups	Outcomes	Conclusion
Chandra, 2016[46]	Retrospective cohort	CRS and comorbid asthma	25 Omalizumab	ATB and steroid use	Mean ATB prescription/month decreased by 37% ($P = 0.013$)
Gevaert, 2013[24]	RDBCP	CRSwNP and comorbid asthma	16 Omalizumab 8 placebo	SF-36, TPS, Lund-Mackay	Significant improvement all outcomes
Tajiri, 2013[47]	Prospective uncontrolled	Eosinophilic CRSwNP and comorbid asthma	6 Omalizumab	SNOT-20 AQLQ, Lund-Mackay	Significant improvement all outcomes
Pinto 2010[25]	RDBCP	Refractory CRSwNP (12/14) or CRSsP (2/14)	7 Omalizumab 7 placebo	UPSIT, SNOT-20, NPS, CT opacification	Significant improvement in CT opacification score, but not for NPS or Sx
Vennera, 2011[48]	Retrospective cohort	CRSwNP and comorbid asthma	19 Omalizumab	NPS	Significant improvement in NPS ($P = 0.035$) and reduction in INCS use ($P = 0.002$)
Penn, 2007[49]	Retrospective case-control	CRSwNP and asthma	4 Omalizumab 4 historically matched controls	NPS and Lund Mackay	Significant improvement in NPS, but not for Lund Mackay scores

RDBPC: randomized double-blind placebo-controlled; CRSwNP: chronic rhinosinusitis with nasal polyposis; SF-36, short-form health questionnaire; Sx: symptom; NPS: nasal polyp score; UPSIT: University of Pennsylvania smell identification test; AQLQ: asthma quality of life questionnaire; INCS: intranasal corticosteroid.

trials. Gevaert et al[24] evaluated 24 CRSwNP patients and found a significant decrease in nasal polyp score (NPS) after 16 weeks of treatment (-2.67, $P = 0.001$). Improvements in nasal and asthma symptom scores were also observed. In the other study, Pinto et al[25] evaluated 14 patients comprised of both CRSwNP and CRSsNP patients and found no significant difference between treatment groups in regard to radiographic scores, nasal peak inspiratory flow, or University of Pennsylvania Smell Identification Test (UPSIT) scores although SNOT-20 scores did improve in the omalizumab group compared to placebo. A recent meta-analysis found no statistical reduction in NPS compared with placebo, although there was a trend toward overall improvement (-0.75; 95%*CI*, -1.93 to 0.44; $P = 0.22$). [26] When post-hoc analysis was done to include only studies in which patients had concomitant severe asthma, a statistically significant reduction in NPS was observed (-1.38; 95% *CI*, -2.22 to -0.44; $P = 0.001$). Overall, the clinical benefits appear to be modest, yet some patients have a better clinical response than others, which delineates the importance of endotype-driven therapies.[27,28] Biomarkers and larger clinical trials are needed to identify potential responders to this therapy and a phase 3 trial is underway.

Anti-IL-5 monoclonal antibody therapy

Since IL-5 is a key cytokine in the activation, chemotaxis, and survival of eosinophils, anti-IL-5 therapies have been developed that either bind free IL-5 or inhibit the IL-5 receptor (IL-5R subunit a) on the surface of eosinophils. Mepolizumab and reslizumab bind free IL-5 while benralizumab inhibits the IL-5 receptor.[29] Mepolizumab, (Nucala) was approved in 2015, reslizumab (Cinqair) in 2016, and benralizumab (Fasenra) in 2017 for the treatment of severe uncontrolled asthma with an eosinophilic subtype. Three RDBPC trials have been published evaluating mepolizumab and reslizumab (Table 2). Gevaert et al[30] conducted a study of 30 CRSwNP patients with mepolizumab. All patients had CRS refractory to topical steroid therapy after surgery. Sixty percent of the patients in the treatment arm had improved polyp and CT scores compared to 10% in placebo group. The most common reported adverse event was the common cold (6/20), but comparison with the placebo group did not reach statistical significance. Bachert et al[29] completed a larger RDBPC study using mepolizumab. One hundred and five patients with recurrent CRSwNP after surgery were included. The treatment group had a greater proportion of patients no longer meeting the criteria for revision surgery compared to placebo ($P = 0.006$). They also found reduced nasal polyposis severity (VAS), improved endoscopic nasal polyp score and SNOT-22. Interestingly, at 4 weeks after the final dose, patients were found to have sustained benefits. In 2006, Gevaert et al[31] published a study of 24 patients in a RDBPC trial using a single dose of reslizumab. There was a significant reduction in nasal polyp score at 4 weeks in the treatment group. Higher nasal secretion levels of IL-5 were found to correlate with better clinical response to therapy. Several phase 3 trials are underway for anti-IL5 therapy in CRSwNP including

Table 2 Summary of published clinical trials using anti IL-5 therapy.

Author, year	Study design	Population	Treatment groups	Outcomes	Conclusion
Bachert, 2017[29]	RDBPC	Refractory CRSwNP	54 Mepolizumab 51 Placebo	Need for revision surgery, NPS, VAS symptoms score, SNOT-22	Reduced need for surgery, reduced NPS and SNOT-22
Gevaert, 2011[30]	RDBPC	Refractory CRSwNP	20 Mepolizumab 10 Placebo	NPS, VAS symptoms, Lund Mackay, Eos and IL-5 serum levels	Reduction in NPS and Lund Mackay scores. Reduced serum Eos and IL-5 levels
Gevaert, 2006[31]	RDBPC	CRSwNP	8 Reslizumab (1 mg/kg) 8 Reslizumab (3 mg/kg) 8 Placebo	NPS Local and peripheral IL-5 levels Eos levels	Responders had increased IL-5 concentrations in nasal secretions at baseline compared with non responders

RDBPC: randomized double-blind placebo-controlled; CRSwNP: chronic rhinosinusitis with nasal polyposis; NPS: nasal polyp score; Eos: eosinophil; VAS: visual analog scale.

those that bind free IL-5 and a monoclonal antibody (benralizumab) that inhibits the receptor.

Anti-IL-4/IL-13 monoclonal antibody therapy

IL-4 and IL-13 exert their inflammatory responses via two separate receptors that both contain the α subunit of the IL-4 receptor. The type I receptor, activated by IL-4, is involved in B-cell activation/expansion, class switching to IgE, Th2 cell differentiation, and recruitment of monocytes as well as eosinophils. Type II receptors can be activated by both IL-4 and IL-13 and induce goblet cell hyperplasia resulting in mucous secretion as well as B-cell activation, IgE production, and recruitment of mastcells and eosinophils. Dupilumab is a human IgG4 monoclonal antibody targeting the α subunit of the IL-4 receptor which results in dual blockade of both IL4 and IL13 signal transduction.[32] A phase II double-blind placebo-controlled randomized study evaluating dupilumab in 60 patients with CRSwNP ($n = 35$ with asthma, $n = 25$ without asthma) showed significant improvements in both objective and subjective measures of disease severity. Patients underwent a run-in period of topical mometasone for four weeks and then underwent either 300 mg of dupilumab subcutaneously weekly or placebo for 16 weeks with a 600 mg loading dose. Patients must have failed at least 2 months of a trial of topical nasal steroids with greater or equal to 2 symptoms of CRSwNP and bilateral nasal polyps on endoscopy meeting scoring criteria (at least an NPS score of 5/8 with at least 2 bilaterally on a 0 to 4 point scale). There was a significant change in NPS of -1.6 points (-29.8%, $P = 0009$), LMK score of -8.8 points (-52.6%, $P < 0.0001$), SNOT-22 change of -18.1 points (-49.2%, $P < 0.0001$), and an UPSIT change of 14.1 ($P < 0.0001$). An example of response to therapy is seen in Fig. 1. In patients with asthma, dupilumab improved FEV1% predicted (7.2% increase; $P = 0.04$) and asthma control (1.1 unit reduction ACQ5; $P < 0.0001$). There was also a decrease in total IgE ($P < 0.0001$) and eotaxin-3 ($P < 0.0001$). Adverse events included injection site reactions headache, and nasopharyngitis. A phase 3 trial is underway for dupilumab in the treatment of CRSwNP. Dupilumab, with the tradename Dupixent was approved in 2017 for the treatment of moderate-to-severeatopic dermatitis and is also investigated for persistent, uncontrolled asthma.[32,33] These studies suggest the importance of IL-4 and IL-13 in chronic inflammatory disorders such as asthma, atopic dermatitis, and CRSwNP. Interestingly, the pathology of nasal polyps in a subset of patients maybe more similar to the Th2-driven immune dysfunction seen in the skin than in the lung considering preliminary observations seen in response to therapy.

Siglec-8 monoclonal antibody therapy

AK001 is an IgG4 monoclonal antibody directed against Siglec (sialic acid-binding immunoglobulin-type lectin)-8. This receptor is found on the surface of mast cells, eosinophils, and basophils and exerts inhibitory activity. As a result, binding the receptor can lead to selective apoptosis of cytokine-primed cells. In mast cells, engagement of Siglec-8 inhibits the activity of FcεRI, downregulating the release of inflammatory mediators such as histamine and prostaglandin D2.[34] In a phase 2 study of 40 CRSwNP patients were randomized to either the treatment group in combination with an intra nasal corticosteroids compared to placebo within tranasal corticosteroid. The medication was administered in IV formulation. The phase 2 study has been competed and analysis is under way.

Anti-TSLP monoclonal antibody therapy

The majority of biologic therapy has first been trialed in asthma prior to application in CRS. Tezepelumab is an IgG2 monoclonal antibody that binds free TSLP and has shown to significantly decrease asthma exacerbation rates.[35] TSLP is a cytokine derived from the epithelium in response to external stimuli and facilitates differentiation of Th2 cells from naive T-cells, augmenting the release of IL-4, IL-5, and IL-13. TSLP acts on dendritic cells, T-cells, B-cells, and ILCs. The phase 2 trial of tezepelumab evaluated low (70 mg, $n = 145$), medium (210 mg, $n = 145$), and high-dose (280 mg, $n = 146$) therapy every four weeks. There was a lower annualized asthma exacerbation rates at week 52 across all treatment groups of 0.26, 0.19, and 0.22 respectively compared with 0.67 in the placebo group

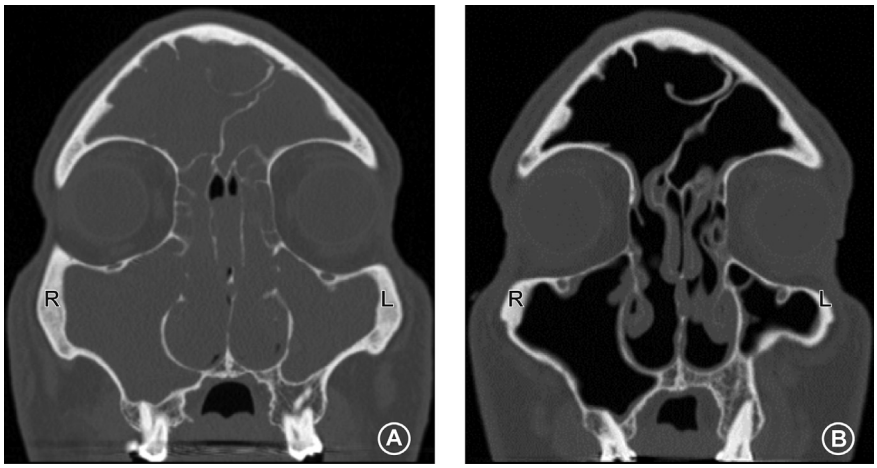

Fig. 1 CT scan of one patient before and after therapy of dupilumab. A: before therapy; B: after therapy.

($n = 148$). This translated to a reduction of asthma exaerbation by 61%, 71%, and 66% compared to placebo ($P < 0.001$) regardless of eosinophil count. It is possible that anti-TSLP therapy in CRSwNP may also be effective since TSLP mRNA has been detected in nasal polyp tissue although no trial is on going at present.[12,36]

Small molecule therapies

Compared to biological drugs which are complex high molecular weight molecules that are usually produced in living cell cultures and potentially immunogenic, small molecule drugs are low molecular weight, produced by chemical synthesis, and are for the most part, non-immunogenic (i.e., aspirin). There has been recent interest in targeting chemokines such as CCR3 which is the primary eotaxin receptor. Other potential chemokine receptors include CCR4, CCR8, CXCR3.

Dexpamipraxole is a non-dopamin ergicenatiomer of the Parkinson's drug, pramipexole. It has a low molecular weight (211.1), is 98% bioavailable, and renally excreted. In amyotrophic lateral sclerosis, approximately 1000 patients who showed a dose- and time-dependent eosinophil- and basophil-lowering activity. This was apparent at 1 month of therapy and at 3–4 months to reach maximum effect. An open-label proof of concept clinical trial utilizing oral dexpramipexole 150 mg twice daily for 6 months was conducted. Inclusion criteria included a nasal polyp score of at least 4 with a unilateral score of greater or equal to 2 on a 0–4 point scale with an eosinophil count of >300 cells/micro Liter. Thirteen of 16 patients completed treatment. Baseline eosinophil count was 525 and decreased to 31 at 6 months, a 94% reduction ($P = 0.001$). In 12 patients who underwent polyp biopsy, tissue eosinophils reduced from a mean of 168 ± 134 to 5 ± 2 eosinophils per high power field ($P = 0.001$), a 97% reduction from baseline. Interestingly, although there was significant reduction in serum and tissue eosinophilia, there was no change in NPS or other clinical end points. There were no drug-related serious adverse events (accepted for publication *Laryngoscope* August 20, 2018).

Cytokines and Fc fusion proteins may also serve as targets in the future for the treatment of CRS either by recombinant therapies, competitive inhibition, or direct receptor stimulation. RNA molecules also show promise using small double-stranded RNA, antisense oligonucleotides, kinase inhibitors, and antichemokine strategies. These strategies have not yet made their way into the treatment of CRS but it is possible that targeting these inflammatory pathways maybe effective.

Discussion

Advanced immunomodulatory therapies are just on the horizon for the treatment of CRSwNP. We are at the cusp of a paradigm shift in conceptualizing treatment of CRSwNP, especially eosinophilic disease, as not a surgical one but perhaps in some patients better managed with medications alone or in combination with an immunomodulatory therapy.

Omalizumab, mepolizumab, reslizumab, and benralizumab are FDA approved (2003, 2015, 2016, and 2017 respectively) for the treatment of severe subsets of asthma (allergic or concomitant eosinophilia) and dupilumab as a treatment for moderate-to-severe atopic dermatitis (2017). The safety of biologic therapies has been investigated mainly in the asthma literature.[37] Omalizumab is the oldest biologic therapy studied and the two main concerns have been the risk of anaphylaxis, which has a reported rate of 0.09% as well as malignancy.[38,39] The Omalizumab Joint Task Force (OJTF) recommends that informed consent should be obtained, a pre-injection health assessment and anaphylaxis education should be performed, an epinephrine autoinjector should be provided and patients should be observed for predetermined duration after injections. Intradermal skin testing can now be performed safely prior to treatment initiation to further stratify risk.[38,40] Monoclonal antibody therapies are associated with a theoretical increased risk of malignancy. The EXCELS study (evaluating clinical effectiveness and long-term safety in patients with moderate to severe asthma) assessed the risk for long-term malignancy in omalizumab-treated patient and concluded that omalizumab was not associated with an increased risk of malignancy.[41] In the largest monoclonal antibody study for CRSwNP treated with mepolizumab, the most common

(greater than 5% incidence) reported adverse events in the largest available study were oropharyngeal pain, back pain, influenza, and pyrexia in the treatment group compared to placebo.[29]

Although there is an explosion of biologics and a keen interest to determine whether monoclonal antibodies will change the course of disease in eosinophilic CRS, the future holds the possibility of other strategies that are endotype specific, effective, safe, and affordable. The cost-effectiveness of these therapies has only been studied in the asthma population, and remains controversial in CRS. Two studies have shown that benefits outweigh the cost of omalizumab in treatment of asthma.[42,43] Cost-effectiveness of mepolizumab remains controversial, and it was estimated that its price should be reduced by 60% for this drug to become cost-effective.[44,45] Ultimately, although we have a working knowledge of the end state of CRS, characterized by loss of olfaction, dysfunction in mucociliary clearance, and development of polyposis, the understanding of the triggers, modifiers, and the plethora of inflammatory pathways is still not completely understood. The epithelial dysfunction in conjunction with immune predisposition, other genetic as well as environmental factors need to be investigated in more detail if we are to prevent or reverse the inflammatory cascade. Immunomodulators will hopefully restore the balance in the constitutive up-regulation of inflammation, which ranges from local to systemic.

Conclusion

Targeted immunomodulatory therapies have the potential to effectively control inflammation in CRSwNP. Several studies have now demonstrated clinical benefit of biologic therapy in the setting of refractory CRSwNP. These new molecules targeting Th-2 cytokines have helped elucidate the behavior and spectrum of CRSwNP, yet no consensus exists on how these therapeutics will fit into the armamentarium of the otolaryngologist managing this disease. Characterization of endotypes, biomarkers and other patient-centered factors are needed that will guide treatment decisions. Phase III clinical trials are currently being performed, which will hopefully mirror advances in understanding the pathomechanism of CRS.

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