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Contemporary Pharmacotherapy for Allergic Rhinitis and Chronic Rhinosinusitis

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Abstract

Chronic rhinosinusitis (CRS) and allergic rhinitis (AR) are chronic conditions causing nasal inflammation. CRS is increasingly recognized as a chronic inflammatory process rather than a chronic infection. It is clinically classified based on the presence of nasal polyps into CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP). While the primary initiating factors in CRS remain unclear, AR is driven by IgE mediated hypersensitivity to environmental allergens. Understanding the underlying inflammatory pathways and disease endotypes are driving innovation toward novel pharmacotherapies targeting critical mediators implicated in CRS and AR including IL-4, IL-13, IL-5, IgE, epithelial initiators IL-33 and TSLP. Many of these new agents have shown promise in RCTs or are being investigated in ongoing RCTs although none have approval for AR or CRS indications yet. Extensive investigations are still needed to determine the role, timing, predictive prognostic factors and long-term safety and efficacy of these agents.

Keywords

Chronic Rhinosinusitis (CRS); Type 2 inflammation; Novel pharmacotherapy; biologics; Immune specific targeting

Introduction

Chronic Rhinosinusitis (CRS) is an inflammatory disease of the nasal airways and paranasal sinuses. The condition is defined by greater than 12 weeks of nasal obstruction, nasal discharge, facial pain/pressure, and reduced/lost smell, combined with either computed tomography (CT) or endoscopic examination with evidence of inflammation, polyps or purulence.^{1,2} In population-based surveys of European and United States populations, between 10.9–11.9% of respondents had CRS-appropriate symptoms although the percentage of these with CT or endoscopic evidence of inflammation remains undefined.^{3,4}

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The most recent consensus statements both from US and European authorities posit that current evidence suggests CRS is a chronic inflammatory process mediated by a complex interplay of environmental and genetic factors that are not fully elucidated.^{1,2}

CRS is commonly further classified into two subsets based on its clinical phenotype, those with polyps (CRSwNP) and those without (CRSSNP). The CRSSNP subgroup exhibits a wide variation in symptomatic and objective manifestations, but those with CRSwNP typically have more severe radiographic disease that can be resistant to conventional medical and surgical therapeutic measures. While convenient, this classification has proven overly simplistic since it does not fully reflect the disease course. For example, there is a subset of CRSwNP patients who have aspirin exacerbated respiratory disease (AERD), which is well recognized to be frequently recalcitrant to medical and surgical treatments.⁵⁻⁸ In order to define pathobiologically coherent disease subtypes in CRS, there has been an evolution from subtyping using clinical characteristics (e.g. presence of polyps, atopy or asthma) to one based on the specific immunologic pathways driving the disease.⁹⁻¹¹

Allergic Rhinitis (AR) is similarly an inflammatory disorder characterized by symptoms of rhinitis including rhinorrhea, blockage, sneezing, or itching following exposure to an environmental allergen to which the patient is sensitized. Typical allergens include dust mites, grass, tree, or weed pollens, cats, dogs and molds^{12,13} and hypersensitivity is detected by skin or serum testing. AR has a significant effect on patient QoL additionally it is often comorbid to and contributes to the development and progression of asthma.¹² While prior studies do demonstrate patients with CRS do have an elevated prevalence of AR, AR is far from universal among CRS patients.^{14,15} Furthermore, exposure studies demonstrate that the changes in the sinuses following allergen exposure are relatively mild compared to those observed in CRS.¹⁶

Inflammatory pathways in CRS and AR

In Western countries, CRSwNP has been associated with type 2 inflammatory responses characterized by eosinophils, mast cells and basophils, elevated total IgE and cytokines including IL-5, IL-4 and IL-13.^{9,11,17-19} Classically, the initiation of type 2 inflammation was postulated to begin with allergen/antigen uptake by dendritic cells that processed the antigens and influenced the T-cell response through the production of cytokines including IL-4 that differentiated Th0 cells into Th2 lymphocytes.²⁰⁻²³ More recently, epithelial cells have been shown to have innate responses that can directly activate a class of lymphocytes called innate lymphoid cells (ILCs) that produce many of the same cytokines traditionally ascribed to T-cells. For example, epithelial exposure to irritants, and antigens induces epithelial production of one or a combination of these initiators, IL-25, IL-33 and TSLP that can directly activate innate lymphoid 2 cells (ILC2 cells) that produce the key pathogenic type 2 cytokines IL-5, IL-13 and to a lesser extent IL-4.²⁰⁻²⁵ IL-5 primarily facilitates differentiation, migration, activation and survival of eosinophils, B-cells and basophils^{26,27} IL-13 which shares a common receptor with IL-4, is thought to have larger effects on structural cells causing epithelial cells to produce mucus and smooth muscle hyper-reactivity.²⁸ IL-4 influences cells of the adaptive immune system driving Th0 to Th2 cell differentiation and B-cell isotype switching and the production and secretion of antibodies.

Of these factors IL-5, IL-13 and the initiator TSLP have consistently been demonstrated to be elevated in CRSwNP nasal tissue whereas elevated IL-4, IL-33 and IL-25 have less consistent data in the CRSwNP patient population.^{29,30} However this pattern may further vary with ethnicity or geography, since over half of Chinese patients are noted to have a non-eosinophilic inflammation.^{11,17,31} We recommend referencing a recent review by Schleimer for an excellent review of type 2 inflammation in CRSwNP.³²

While CRSsNP was traditionally described as a type 1 inflammatory response with elevated neutrophils, lower levels of eosinophils, this view has been challenged by two recent publications that find that it is a heterogeneous inflammatory response with Type 1, 2 and 3 responses.^{1,10,11,17} These studies also demonstrate that in Western countries, approximately 30–50% of patients with CRSsNP have elevated markers of type 2 inflammation similar to CRSwNP making this the most common endotype found in CRSsNP. There were also minor but significant subsets of patients with CRSsNP that had elevated IL-17 (4–25%) and IFN- γ (6–21%) in their nasal mucosa.^{1,10,18} Clearly further research is still needed to understand the interplay of these pathways with correlations to disease phenotypes, treatment responsiveness and prognosis.

While many of the same type 2 mediators, effector cells and cytokines found in CRS are also found in AR a fundamental difference is AR is triggered by an IgE dependent mast cell degranulation due to exposure to a specific antigen that the patient has a previously developed systemic atopic hypersensitivity.³³ In the late phase following allergen exposure, recruitment of other effector cells including eosinophils and Th2 cells can be found.^{13,34} However, atopy does not significantly influence symptom severity, extent of sinus disease on CT scans and likelihood of undergoing revision surgery among CRS patients.³⁵

Conventional CRS and AR treatment

The controversy over the pathologic underpinnings of CRS lead to significant variability in how CRS is cared for medically. Currently, intranasal saline irrigations, topical intranasal steroids, oral steroids and surgical management when medical therapy fails represent contemporary care options for which evidence of efficacy exists.^{1,2} Topical saline irrigations have been shown to reduce symptom scores when used as sole agents or adjuncts to intranasal steroids.³⁶ The efficacy of topical intranasal steroids has been substantiated in RCTs in AR and meta-analysis of RCTs of CRSsNP and CRSwNP with evidence for modest improvements in symptom outcome scores, and polyp size reduction especially in those that had previously undergone surgery.^{37–42} Short courses of systemic steroids have also been well studied in CRSwNP showing improvements in polyp size, symptoms and outcomes.^{43–45} There is no high level evidence supporting the use of systemic steroids in CRSsNP although they are likely to be effective in the subset of patients who have elevated type 2 inflammation.⁴⁶ Despite almost universal prescription for CRS care, strong evidence for the efficacy of antibiotics is still lacking. Overall, recent consensus statements indicate against or insufficient evidence for non-macrolide oral antibiotics.^{1,2} Additionally, long term macrolide therapy that have been studied in two randomized, placebo controlled studies drew mixed conclusions with one study showing a benefit and another with no benefit likely due to differential recruitment of CRSwNP and post surgical patients in the two studies.^{47–49}

The use of intranasal and oral second-generation antihistamines remains first line therapy for intermittent AR but not in CRS.^{34,50} In CRS, leukotriene inhibitors have a slight inferiority as a single modality to prevent nasal polyp recurrence compared to other agents such as intranasal steroids.^{51,52} In AR, leukotriene inhibitors are also inferior in symptom control compared to intranasal steroids and antihistamines however these agents could be considered for dual therapy of patients with persistent asthma.⁵⁰ Therefore current recommendations are against routine use of leukotriene inhibitors for CRS and AR as first line agents.^{1,2,50}

Studies in AR patients show that proper implementation of ARIA guidelines can result in symptom control in 80–90% of patients.^{53,54} By contrast, despite implementation of “appropriate medical therapy” rates of symptomatic improvement are modest and variable (38%–51%) in CRS depending on the threshold of success, symptom domain and duration of follow up.^{17,55,56} CRS patients failing appropriate medical therapy are offered endoscopic sinus surgery that has been shown in prospective observational studies to deliver significantly increased quality of life compared to continued medical management.^{57,58} In fact, emerging evidence suggests earlier surgical intervention may prevent the development of adult onset asthma.^{58,59} However there still remain recalcitrant patients in high-risk groups particularly those with nasal polyps (AERD, eosinophilic mucin, comorbid asthma) that either do not respond to medical or surgical interventions or have co-morbidities for which these interventions are contraindicated.

Thus, unlike other atopic airway diseases like asthma or AR, CRS uniquely has a minimally invasive surgical management option with demonstrated efficacy. Thus, when considering the role of pharmacotherapy in CRS, we propose that evidence for its efficacy may increasingly be judged on the basis of its intended purpose and temporal association with surgery. This nomenclature well developed in oncology where both medical and surgical treatments are critical to the standard of care but have, to our knowledge, not been applied in CRS care. Thus, “induction” pharmacotherapy may be used to induce a remission of CRS without surgery, “adjuvant” pharmacotherapy may be applied around the time of surgery to enhance the chance of remission, “maintenance” pharmacotherapy may be used to sustain a remission and “salvage” pharmacotherapy may be applied when conventional medical and surgical options have failed. While many prior pharmacotherapy studies of CRS were used for induction, the more recent “biologics” have been studied in CRS largely in the context of salvage treatment for CRSwNP (Figure 1 and Table 1).

Biologic therapy in Chronic Rhinosinusitis

IL-5 pathway

Reslizumab—The earliest randomized clinical trial (RCT) using biologics was published in 2006 using reslizumab (humanized anti-IL5) for CRSwNP patients with bilateral grade 3 or 4 nasal polyps or recurrent nasal polyps after surgery. This agent was recently FDA approved in 2016 for add on maintenance treatment of severe eosinophilic asthma. IL-5 has been found to be elevated in nasal polyp tissue compared to normal controls, with the highest concentrations in patients with comorbid nonallergic asthma or AERD.^{60,61} A total of 24 patients were enrolled and divided to receive placebo, or a single 1mg/kg or a 3mg/kg intravenous dose. Reslizumab was well tolerated in patients with most common adverse

event being URI symptoms. In the active treatment groups, the investigators found polyp size improved in about half of the patients at 4 weeks but 4 patients had deterioration in polyp scores by 12 weeks. Nasal peak inspiratory flow rates (NPIF) and symptoms were not different at any time point. Biologic activity analysis showed peripheral eosinophil counts, peripheral and local IL-5 levels, and eosinophil cationic protein (ECP) levels decreased up to the 8-week time point but peripheral eosinophil counts rebounded to higher levels by 24 and 32 weeks. As a phase 1 trial, the study was underpowered to detect the difference in polyp size, or symptoms. However, in comparing baseline characteristics of responders to non-responders they noted that the responders had higher baseline nasal IL-5 levels, alluding to a possible role for nasal IL-5 in predicting responders.⁶²

Mepolizumab—Mepolizumab, another anti-IL5 humanized antibody that was FDA approved for severe eosinophilic asthma in 2015, has been investigated in CRS. Twenty CRSwNP patients (grade 3 or 4 or recurrent after surgery) were given two 750mg doses 28 days apart and results were compared to 10 patients that were given placebo. This trial was better powered to assess the efficacy of anti-IL5 treatment compared to the previous study of reslizumab by the same group. Sixty percent of the treated group compared to 10% of the placebo group had improvements in the primary endpoint of nasal polyps scores at 8 weeks. There were also significant improvements in the secondary endpoints of radiographic severity, blood eosinophil levels, ECP, blood IL-5R levels at 8 weeks. Patients also noted decreased post nasal drip, better smell, and congestion at 8 weeks but rhinorrhea was unaffected. Interestingly the responders were not noted to have elevated nasal IL-5 levels nor was a robust rebound eosinophilia noted.⁶³ In review of the clinical trials registry, it appears that an additional study of mepolizumab has recently completed recruitment of 105 patients with CRSwNP refractory to medical and surgical therapy with the primary endpoint being the need for surgery after treatment.⁶⁴

Benralizumab—Another agent that could potentially have some promise for inhibiting the IL-5 pathway in CRS is benralizumab. Most recently a 2016 phase 3 RCT in refractory eosinophilic asthma patients showed that those treated had higher prebronchodilator FEV1 and lower annual asthma exacerbation rates.⁶⁵ This agent works by competitively inhibiting the IL-5 receptor and due to a fucosylation of the monoclonal antibody, it more strongly binds NK cell receptors causing an antibody-dependent, cell-mediated cytotoxicity of effector cells including eosinophils and basophils which have also been implicated in CRSwNP.^{27,66} Currently there is an ongoing phase 2 RCT of subcutaneous administration of benralizumab in eosinophilic chronic sinusitis that is estimated to be completed in October 2017.⁶⁷

IgE pathway

Omalizumab—Omalizumab is a humanized anti-IgE monoclonal antibody that binds free IgE preventing binding to receptors on mast cells and basophils. Previous studies have shown that this agent can also decrease IgE receptors on effector cells.⁶⁸ Omalizumab was approved for treatment of severe allergic asthma in 2003.

Of the biological agents discussed, omalizumab is the only agent that has been studied for AR treatment. In 2000, a European study randomly assigned 251 patients with seasonal AR with positive testing to birch pollen to receive omalizumab vs placebo. They noted significantly decreased serum IgE levels, improved average daily nasal symptom scores, QoL questionnaires and decreased use of rescue antihistamines.⁶⁹ These findings were again noted in a dose-dependent fashion in a second RCT of 536 patients with ragweed-induced seasonal AR.⁷⁰ A separate RCT of 289 patients with perennial AR also noted symptomatic improvement relative to placebo.⁷¹ Despite demonstrated efficacy, the use of omalizumab in the AR patient population remains limited to those with severe disease and comorbid severe allergic asthma due to the high cost and lack of an AR indication for this drug.³⁴

Evidence for efficacy of omalizumab has been reported in case series and case reports of CRSwNP patients with comorbid asthma. These studies showed significantly reduced endoscopic nasal polyp scores at 16 weeks and decreased intranasal steroid use from 95% to 42% at the end of follow up.^{72,73} It should be noted that omalizumab in these cases was generally applied in a “salvage” situation as patients all had failed medical and surgical management of their CRSwNP.

The first RCT evaluating omalizumab in CRS patients was published in 2010. Fourteen patients (12 with CRSwNP and 2 CRSsNP) were randomized to receive placebo or subcutaneous omalizumab every 4 weeks for 6 months. Interestingly, the study suffered from poor recruitment and patients were allowed to continue previous treatment regimens. Although they were similar at baseline, these factors limited the study’s ability to assess efficacy of omalizumab in “induction” therapy. This study found radiographic opacification did significantly decrease modestly from 76.1% to 60% pre- to post- omalizumab treatment but similar changes were not observed in the placebo arm. However, there was no significant difference in any of the secondary outcomes including nasal endoscopy scores, SNOT-20 scores, UPSIT olfactory testing, NPIF testing and eosinophil levels in nasal lavage. Patients in the trial were also allowed to use “rescue” medications during the trial period and it was noted that the omalizumab group needed fewer systemic steroid treatments.⁷⁴

The second omalizumab RCT was published in 2014 where 24 allergic and nonallergic patients with CRSwNP and comorbid asthma were 2:1 randomized to receive 4–8 doses of Omalizumab subcutaneously or placebo. Unlike the prior study, patients in the treatment arm were noted to have significantly decreased endoscopic nasal polyp scores and Lund Mackay CT scores. Secondary outcomes of improved asthma QoL measures and nasal symptom questionnaires were noted in the omalizumab treated patients. Interestingly both allergic and nonallergic patients noted significant improvement in outcomes indicating that local IgE may play a role in mediating the inflammatory process in non allergic patients.⁷⁵

Lastly, Chandra et al retrospectively examined a series of 25 patients with asthma and CRS, where 8 of the 25 had CRSwNP. They assessed the antibiotic and steroid use in patients prior to and after treatment with omalizumab. Their analysis specifically looked at prescriptions given for CRS or CRS with asthma exacerbations, and excluded those for asthma alone. They noted a statistically significant 60% reduction in the use of antibiotics in

their series. The study also noted a non statistically significant 42% reduction in systemic steroid use.⁷⁶

While generally safe, omalizumab is associated with some concerns about anaphylaxis, and malignancy, side effects. The anaphylaxis risk, as assessed by the omalizumab joint task force (OJTF), was 0.09%. The OJTF thus recommends an observation period in clinic after administration and patients should be given precautions for signs and symptoms of anaphylaxis and an epinephrine auto-injector.^{77–79} After a 2003 asthma omalizumab trial there was a numerical imbalance of malignancy rates (primarily non-melanoma skin cancers and other solid tumors) of 0.5% compared to 0.2% in the placebo group.⁸⁰ In a larger study, 7857 asthmatic subjects with 5004 omalizumab treated patients were compared with non-omalizumab treated patients and found no difference in malignancy rates.⁸¹ However, the cohort had poor follow-up and excluded of patients with prior cancer history.⁸²

IL-4/13 pathway

Dupilumab—Another studied pathway for which RCT data exists in CRS is the IL-4/13 pathway. While prior studies evaluating antibodies against IL-4 or -13 have been disappointing in asthma⁸³, IL-4 and IL-13 receptor share a common alpha subunit which make blockade of the receptor an attractive target. Dupilumab is an anti-IL-4/13 alpha subunit receptor antibody that has just been approved for atopic dermatitis. In a very recent RCT, sixty CRSwNP patients were enrolled (35 also had comorbid asthma) with a 1:1 randomization to dupilumab or placebo for 16 weeks. Patients also continued intranasal steroid therapy. They noted at least a 1 point polyp score improvement in 70% of treated patients compared to 20% in the placebo group at the 16-week endpoint, and this difference was apparent as early as the 4 week timepoint. Significant improvement was also noted in Lund-Mackay CT scores, percent maxillary sinus opacification, NPIF scores, symptom scores, SNOT-22 and UPSIT olfactory scores compared to placebo treated patients. Decreased levels of serum total IgE levels and eotaxin-3 levels were noted in the patients receiving dupilumab. The most common side effects noted were nasopharyngitis, headache, and injection site reactions.⁸⁴

Other ongoing studies in CRS

Siglec-8 Targeting

Siglecs, which stands for sialic acid-binding immunoglobulin-like lectins, are a family of transmembrane glycoproteins that activate intracellular pathways.⁸⁵ Siglec-8, is specific to the surface of human eosinophils, mast cells and basophils.⁸⁶ Binding of antibody to siglec-8 has been shown in in-vitro studies to induce apoptosis in cytokine-activated eosinophils or preventing release of mediators from mast cells.⁸⁷ This provides a unique method of inhibition of these target cells in CRS.⁸⁸ There is currently a phase 2 RCT with the drug AK001 in CRSwNP patients.⁸⁹

IL-33 Targeting

Another epithelial derived cytokine that has been showed to be elevated in nasal polyps at the gene expression level is IL-33.^{90,91} IL-33 influences differentiation and activation of Th2

cells, ILC2 cells, mast cells, basophils and the cytokine IL-13.²⁰ Results are pending results from a phase 1 RCT in 41 patients with CRSwNP and healthy volunteers treated with AMG 282 a monoclonal antibody that inhibits binding of IL-33.⁹²

Other potential targets in CRS

TSLP targeting

As discussed earlier, TSLP is a potent epithelial derived cytokine that stimulates dendritic cell driven Th2 polarization and ILC2 activation that is elevated in nasal polyp tissue.^{21,90,93} Anti-TSLP targeting has shown promise in a recent studies of asthmatics treated with a humanized monoclonal antibody AMG-157. This study found the severity of asthma attacks and blood and sputum eosinophils decreased significantly in the AMG-157 treated arms.⁹⁴ Although there are ongoing clinical trials with AMG 157 for atopic dermatitis and asthma, there are no ongoing clinical trials in CRS patients.

Small molecule inhibitors of the type 2 pathway

There have been a few interesting small molecules specifically targeting Th2 pathways GATA3, CRTH2, and dexamipexole. GATA-3 is a transcription factor that controls the differentiation of Th2 and ILC2 cells that produce IL-4, IL-13, and IL-5. (Table 2)⁹⁵ The GATA-3 DNzyme was designed to penetrate cells and target the GATA-3 RNA for cleavage.^{96,97} A recent phase 2 RCT of SB010 (GATA-3 DNzyme) was used in patients with mild allergic asthma with sputum eosinophilia and showed the drug attenuates early and late phase asthmatic responses after allergen exposure. Biologically this study noted reduced mast cell activation, airway eosinophilia and serum IL-5 levels.⁹⁷ There have yet to be any investigations of this agent in a CRS patient population.

The CRTH2 antagonist OC000459 was studied in asthmatic and AR patients and shown to block the effects of Prostaglandin D2 which contributes to accumulation and activation of Th2 cells, eosinophils and basophils in tissues.^{98–100} Lastly, dexamipexole is an investigational small molecule drug used for amyotrophic lateral sclerosis that incidentally was noted to significantly decrease absolute eosinophil levels. Investigations are underway and have shown some promise in decreasing eosinophil levels in CRS patients.^{101,102}

Challenges with biologics

While treatment with targeted therapy shows promise for CRS treatment, currently FDA approved biological options are costly and do not appear to durably resolve findings or symptoms of CRS after treatment cessation. While CRS is not directly a life-threatening disease, prior studies suggest general quality of life impairment and health utility values are comparable to more serious illnesses. Our prior studies suggest that given average utility values in CRS, treatments that *cure* CRS for less than \$11,000 per year would be cost effective using a willingness to pay threshold of \$50,000 per quality adjusted life year (QALY).¹⁰³ Additionally, the efficacy of these agents has yet to be weighed against the costs and efficacy of conventional medical therapy and endoscopic sinus surgery that is efficacious in a significant fraction of patients.

Given the cost of currently approved biologics (omalizumab and mepolizumab), if cost trends continue, it is likely that biologics will be reserved for salvage therapy for CRSwNP patients with comorbid severe asthma, AERD or recalcitrance after sinus surgery. For biologics to gain a role for induction or maintenance therapy in CRS, it is likely novel pharmacologic agents will have to be relatively inexpensive. Other novel applications of new pharmaceuticals may be their role in an adjuvant setting to help enhance the long-term efficacy of endoscopic sinus surgery. Significantly increased investment in studies of CRS are needed to define the safety, efficacy and role these novel biological drugs will play in the care algorithm.

Summary

Allergic Rhinitis is driven by an IgE mediated hypersensitivity to environmental allergens triggering a Th2 mediated response. Current pharmacotherapy for AR is very effective in symptom control if guidelines are followed and biologic therapies are subsequently less well studied in AR. CRS is increasingly recognized as a chronic inflammatory process rather than a chronic infection. The type 2 endotype is found in the majority of CRSwNP in Western countries and although CRSsNP is heterogeneous, up to 50% have elevated type 2 inflammation. Novel pharmacotherapies developed to target type 2 inflammation in asthma have been applied to CRSwNP demonstrating significant promise. However, further investigations are still needed to determine the role, timing, predictive prognostic factors and long-term effects of these agents.

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Key points

- Chronic rhinosinusitis (CRS) is driven by chronic inflammation of the sinonasal mucosa initiated by undefined factors. In contrast, allergic rhinitis (AR) causes nasal inflammation following nasal exposure to sensitized environmental allergens.
- A type 2 inflammatory response with ILC2 cells, Th2 cells, eosinophils, basophils and mast cells along with the cytokines IL-5 and IL-13 dominates CRS with nasal polyposis and a substantial fraction of patients with CRS without nasal polyps.
- New biologics indicated for asthma have been studied in RCTs of AR and CRS patients and demonstrate efficacy largely in a “salvage” setting.

Figure 1.

Roles for biologic therapy in the treatment of CRS. “Induction” medical therapy – could be combined with appropriate medical therapy, less complications than surgery, and at least as efficacious. “Adjuvant” medical therapy enhances effects and durability of surgery. “Salvage” medical therapy – reduces the need for revision surgery, reserved for patients with recalcitrant disease.

Table 1

Studies of biologics studied in CRS patients

Study	Year	Drug name & Mechanism	Study population	End points	Adverse events	Interesting points or problem with study
Randomized Clinical Trials						
Gevaert P, Calus L et al. ⁷⁵	2013	Omalizumab - Anti-IgE	24 patients - CRSwNP with comorbid asthma	1	Endoscopic Nasal polyp scores	Small sample size. Was effective independent of allergy status or symptom/QoL questionnaires elevated serum IgE.
				2	CT scores	
				3	Nasal and asthma	
Pinto JM et al. ⁷⁴	2010	Omalizumab - Anti-IgE	14 patients - 12 with CRSwNP	1	Lund Mackay Score	Showed minor improvements in radiographic severity. Patients resumed previous therapy and were allowed to have "rescue" medications
				2	SNOT-20	
				3	UPSIT	
				4	NPIF	
				5	Eosinophil levels	
Gevaert P, Lang-Loidolt D et al. ⁶²	2006	Reslizumab - Anti IL-5	24 pts CRSwNP (grade 3-4 or surgical salvage)	1	Endoscopic Nasal polyp scores (qualitative)	Increased baseline IL-5 predicted responsiveness
				2	NPIF	
				3	Serum eosinophilia	
				4	IL-5 levels	
				5	ECP levels	
Gevaert P, Van Bruene N et al. ⁶³	2011	Mepolizumab - Anti-IL-5	30 pts CRSwNP (grade 3-4 or surgical salvage)	1	Endoscopic Nasal polyp scores	Significantly improved symptoms and reduced nasal polyps.
				2	CT scores	
				3	NPIF	
				4	Symptoms	
				5	Serum eosinophilia	
				6	IL-5R levels	
				7	ECP levels	
Bachert C, Mammen L, et al. ⁸⁴	2016	Dupilumab - mAb to IL-4R- α _{subunit}	60 CRSwNP with and without Asthma	1	Endoscopic Nasal polyp scores	Dramatic improvements in symptoms and
				2	CT scores	

Study	Year	Drug name & Mechanism	Study population	End points	Adverse events	Interesting points or problem with study
				3	UPSIT	biomarkers of type 2 inflammation.
				4	NPIF	
				5	SNOT22	
				6	Serum IgE	
				7	IL-5 levels	
				8	Eotaxin-3 levels	
Retrospective studies						
Vennema Mdel C, Picado C et al. ⁷⁵	2011	Omalizumab - Anti-IgE	18 severe asthmatic patients with nasal polyps	1	Endoscopic Nasal polyp scores	
				2	Intranasal steroid use	
Chandra RK, Clavenna M et al. ⁷⁶	2016	Omalizumab - Anti-IgE	25 patients with asthma and CRS	1	Antibiotic use - 60% reduction	
				2	Systemic steroid use - 42% reduction	

Table 2
Studies of other biologics or small molecules targeting type 2 pathways studied in humans

Other agents with prospective applications				
Study	Year	Drug name & Mechanism	Study population	End points
Arm JP, Bottoli I et al.	2014	ligelizumab - Anti IgE	Atopic patients	serum IgE levels
NCT01362244	Ongoing	Mepolizumab - Anti-IL-5	105 CRSwNP patients refractory to conventional therapy	Time to surgery or polyp recurrence after salvage therapy
NCT02772419	Ongoing	Benralizumab - Anti IL5 Receptor	Eosinophilic CRS patients	Will effectively assess duration of action
NCT02734849	Ongoing	AK001 - Anti-Siglec-8	CRSwNP	Phase 2 RCT
NCT02170337	Ongoing	AMG282 - Anti-IL33/ST2 receptor	41 CRSwNP patients and healthy volunteers	1 Safety 2 pharmacokinetics
AMG 157 - Anti TSLP				
only studied in asthmatic and Atopic dermatitis patients				
Small molecule inhibitors of the Type 2 pathway				
SB010 - GATA3 DNzyme				
only studied in asthmatic patients				
NCT02874144	OC000459 - CRTH2 antagonist	AR and asthmatic patients		
Dexpranipexole				
Eosinophil associated diseases, CRS				
Absolute eosinophil levels				