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Acquired Immunity in Chronic Rhinosinusitis

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Abstract Chronic rhinosinusitis (CRS) is a prevalent disease that is associated with significant costs and quality of life impairments. Currently, patients are classified into subgroups based on clinical characteristics, most often the presence or absence of nasal polyps. However, despite medical and surgical treatment, many of these patients continue to have symptoms. Recent efforts have focused on gaining a more complete understanding of the inflammatory mechanisms that drive pathogenesis in CRS, and it is becoming clear that the inflammatory processes in CRS are quite complex. As our understanding of these complex phenotypes improves, it may become possible to classify patients into endotypes based on unique inflammatory patterns within the sinus mucosa. This information may also lead to the identification of appropriate targeted therapies for different endotypes. This review will discuss our current understanding of endotypes in CRS along with the unique adaptive immune responses that may contribute to these different endotypes and, finally, some potential targeted therapeutics for the next generation of CRS treatment strategies.

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Introduction

Chronic rhinosinusitis (CRS) is a chronic disease of the upper respiratory system that affects about 10–12% of the population [1, 2]. Despite the high prevalence, quality of life impairment, and costs associated with CRS, the key inflammatory mechanisms that drive inflammation and persistence in this disease remain unclear. Currently, patients with CRS have limited treatment options; medical management of CRS frequently fails to sufficiently improve symptoms and many patients ultimately have endoscopic sinus surgery to remove inflamed sinus tissues and relieve symptoms [3]. Many researchers have been focused on elucidating these mechanisms with the goal of identifying new treatment options for CRS patients. From this work, it is clear that the inflammatory process in CRS is complex, and it involves multiple arms of the immune response. The goal of this review is to summarize the current knowledge regarding different classifications of CRS patients and how the adaptive immune response plays a role in disease pathogenesis in different subgroups of CRS patients. The innate immune system also plays very important roles in the pathogenesis of CRS, but that topic is beyond the scope of this review and has recently been comprehensively summarized elsewhere [4].

Classification of CRS Patients

Clinical Classifications

CRS is clinically classified into two phenotypes based on the presence or absence of nasal polyps on endoscopic examination: CRS with (CRSwNP) and without (CRSsNP) nasal polyps [1, 5]. CRSwNP can be further divided to include a subset of patients with aspirin-

exacerbated respiratory disease (AERD), which is characterized by severe manifestations of CRSwNP and asthma, in addition to respiratory reactions to aspirin and other inhibitors, such as NSAID, of the COX-1 enzyme [6]. There are additionally rare but unique subsets of CRS that can be attributed to a specific genetic disorders such as cystic fibrosis, a pathogenic organism such the fungal species causing allergic fungal rhinosinusitis, or dental conditions that will not be discussed in this review [5, 7]. Studies suggest that the overall symptom burden of CRSsNP and CRSwNP have significant overlap, with patients in both groups demonstrating similar overall total symptom scores on quality of life instruments. However, it has been suggested that the symptoms that cause the biggest problems for CRS patients are distinct between CRSsNP and CRSwNP groups, with facial pain/pressure, headache, and cough being more bothersome in CRSsNP, whereas CRSwNP patients are significantly more bothered by nasal obstruction and hyposmia/anosmia [8–10]. Given that patients with CRS have relatively few treatment options, and a significant subset of patients do not respond to these treatments, it is important to determine how to tailor treatments to optimize outcomes and reliably identify patients for the treatments best suited to their underlying pathophysiology.

Endotypes of CRS

It is apparent that these current clinical definitions of CRS patient subsets lack complete insight into the pathophysiologic underpinnings of these diseases. Many groups are now investigating whether CRS patients would be better classified on the basis of symptom patterns or using patterns of inflammation measurable within the mucosa or serum to create more specific CRS patient endotypes [11–13]. The proponents of endotyping in CRS suggest it will better identify patients for targeted therapy. Importantly however, currently available and approved treatments for CRS, such as endoscopic sinus surgery or corticosteroids, are effective for many patients, regardless of their inflammatory phenotype. Nonetheless, not all patients respond to these traditional treatments, and longer-term follow-up suggests that CRSwNP phenotype is associated with increased recurrence [14]. Furthermore, exciting new data from clinical trials has demonstrated efficacy for therapies specifically targeting type 2 inflammation in CRSwNP patients providing critical insights into disease pathogenesis (discussed below) [14–16].

Classically, CRSsNP has been characterized by increased levels of type 1 inflammatory mediators, including IFN-γ, while CRSwNP has been characterized by increased levels of type 2 inflammatory mediators, including IL-5 and eosinophils [1, 17]. Recently, two simultaneously published studies, one by our group and the other by an international consortium sampling from five countries across three continents, demonstrated that surgically managed CRSwNP in Western countries (e.g., Germany, Belgium, and the USA) are almost universally (~80–90%) characterized by elevated levels of type 2 cytokines, such as IL-5, IL-13, and eosinophil granule proteins, including eosinophilic cationic protein (ECP) or Charcot Leyden Crystal protein [18, 19]. Unlike the Western populations studied, the Chinese populations studied had significantly less frequent eosinophilia and may have a distinct pathophysiology [19–21]. In contrast, CRSsNP appears endotypically more heterogeneous, with 30–50% of patients exhibiting elevated type 2 inflammation, making it the most common endotype identified. These results were quite surprising, given the long-held tenet that CRSsNP was primarily driven by type 1 inflammation. Moreover, within both types of CRS, there were smaller subsets of patients who had elevated IL-17 (~15%) or IFN-γ (5–23%), particularly within the CRSsNP phenotype (Fig. 1). Together, these findings suggest that CRSwNP is pathobiologically more homogeneous than CRSsNP and that there is a sizable subset of patients with CRSsNP who are *endotypically* similar to patients with CRSwNP. These types of observations further support the concept of endotypic classification of CRS based on the inflammatory patterns found within nasal tissue. In fact, a recent study suggests that endotypes influence the prevalence of comorbidities [22]. However, the number of patients in each endotypic group in this study was small, and whether treatment outcomes or patient symptoms were distinct among the endotypes used remains unclear. Altogether, these studies suggest that endotyping has the potential to predict treatment outcomes and help select more effective therapies in the future, but significant validation of these endotypes will be needed before they can be clinically useful.

Adaptive Immunity in CRS

T Cell Responses

Several groups have investigated the potential role for T cells in CRS (Fig. 1). In fact, T cells appear to be the predominant lymphocyte population in the nasal mucosa from CRS patients, particularly in CRSwNP nasal polyps [23–25]. Early studies that used immunohistochemistry found that CD3+ T cells were increased in both CRSsNP and CRSwNP tissues [26]. More recently, Derycke and colleagues used flow cytometry and intracellular cytokine staining to more fully characterize the T cells in sinus tissues of CRS patients [27]. They found that the frequency of CD3+ T cells was significantly
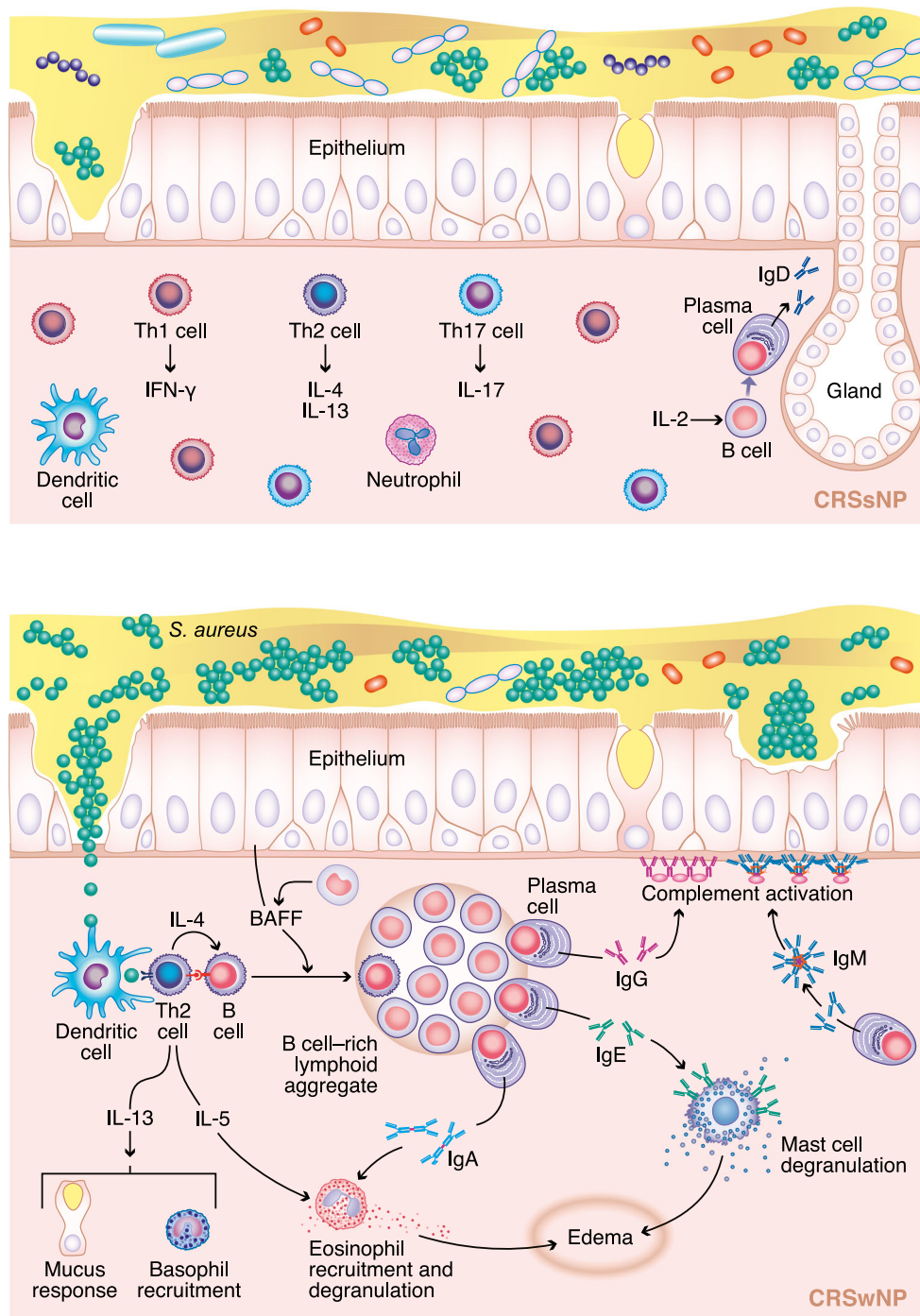
Fig. 1 Adaptive immunity in CRS. CRSsNP (top) is characterized by a mixed inflammatory phenotype. This includes Th1, Th2, and Th17 cells. Cytokines produced by these cells, including IFN-g, IL-4, IL-13, and IL-17, may contribute to chronic inflammation through activation and/or skewing of innate effector cells such as dendritic cells and neutrophils, and these cytokines represent potential therapeutic targets. In addition, IgD-secreting plasma cells are elevated in the nasal mucosa of these patients, and this may be driven by IL-2. CRSwNP (bottom) is characterized by a type 2 inflammatory environment. This includes Th2 cells that produce IL-4, IL-5, and IL-13, all of which are potential therapeutic targets, and can contribute to the activation, recruitment, or skewing of innate effector cells such as dendritic cells, eosinophils, mast cells, and basophils. In addition, there is a large increase in the number of antibody-secreting cells in the nasal mucosa. These cells can produce autoreactive IgG and IgM that can bind to components of the basement membrane and activate compliment, as well as high levels of IgE, another potential therapeutic target. The cytokine BAFF is also elevated in CRSwNP tissues, may be important for local activation of B cells, and could also be a therapeutic target

increased in CRSwNP compared to CRSsNP or control nasal tissue, but they did not find an increased frequency of these cells in CRSsNP compared to control tissue [27]. Interestingly, they reported that Th1 cells, based on IFN-γ staining, were the most common T cell population in CRSwNP, CRSsNP, and control mucosa, but Th2 cells (IL-4 or IL-5 producing $CD3^+CD4^+$ cells) were only detected in CRSwNP tissues. They also detected other heterogeneous populations of T helper cells including Th1, Th22, Th17, and T follicular helper cells in both control and CRS tissues [27]. It is important to keep in mind that these T cell phenotypes were identified from surgically removed tissues, and it remains to be determined whether these T cell profiles can be identified based on the cytokines they produce, which could potentially be measured in nasal lavage fluids. Such studies will be needed before our knowledge of distinct T cell subsets in the nasal mucosa can be used to reliably group patients into a particular endotype for targeted treatment prior to surgery.

In addition to inflammatory T cell subsets, T regulatory cells (Tregs) have also been studied in CRS. Early studies focused on analyzing the gene expression of FoxP3, the master transcriptional regulator of Tregs. These studies found that expression of FoxP3 was decreased, both at the mRNA and protein level, in CRSwNP. They also found decreased expression of the regulatory cytokines IL-10 and TGF-β, suggesting a deficiency or a dysfunction of Tregs in CRSwNP tissues [20, 28]. These findings were further supported in a separate study that found decreased percentages of $FoxP3^+CD8^+$ Tregs in both eosinophilic and non-eosinophilic nasal polyps [29]. In contrast, another study reported that the overall frequencies of $CD4^+$ Tregs ($CD3^+CD4^+CD25^+FoxP3^+$) were significantly higher in CRS tissues compared with controls, while $CD8^+$ Tregs ($CD3^+CD8^+CD25^+FoxP3^+$) were significantly reduced in CRSwNP by means of flow cytometric analysis [30]. Some of the discrepancies in these findings may be due to the fact that in humans FoxP3 is expressed by both Tregs and activated effector T cells. As such, additional markers were needed to accurately identify whether Tregs were responsible for these observations in human tissues. In a study by Miljkovic and colleagues, more specific markers of human Tregs were used to identify these cells in CRS tissues by flow cytometry. In contrast to the prior studies, this study found that Tregs ($CD45^+CD4^+CD25^+CD127^{low}$) were significantly *elevated* in CRSwNP nasal tissue compared to CRSsNP [31]. This suggests that perhaps the Tregs found in CRSwNP tissues are not effective at controlling inflammation in this environment. Importantly, another recent study has suggested that glucocorticoid treatment, which is commonly used to treat CRSwNP, may directly increase the numbers of Tregs ($CD4^+CD25^+CD127^{low}$) in nasal polyp tissue, and thus, concurrent medical treatment may have significantly affected the frequency of Tregs detected [32].

Taken together, even though numerous studies indicate that Tregs play an important role in inflammatory diseases, further studies are needed to delineate the function of Tregs in CRS pathogenesis, as well as the effect of medical treatment on their numbers and function, given the conflicting results in the literature [4, 33].

B Cell Responses

As with T cells, there is mounting evidence that B cells may play and important role in the pathogenesis of CRS, especially in CRSwNP (Fig. 1). B cell activating factor of the TNF family (BAFF) plays a critical role in B cell survival and differentiation to plasma cells, and it has been shown to be highly elevated in nasal polyp tissues [34, 35]. In line with this, early studies demonstrated elevated expression of the B cell marker CD19 and the plasma cell marker CD138 in CRSwNP tissues [26]. In addition, using flow cytometry, we have reported that plasma cells, which are terminally differentiated antibody-secreting cells, are also highly elevated in nasal polyps [36]. More recently, it has been reported that B cell activation events that occur within nasal polyps are distinct from the classical activation mechanisms used in germinal centers, and this difference may be important for the overall increased levels of activated B cell subsets found in nasal polyps [37]. Another recent report has demonstrated that B cells that express CD180, which is an unconventional member of the toll-like receptor family that plays an important role in B cell activation and proliferation, are also elevated in nasal polyps compared to control sinus tissue [38]. Altogether, these data suggest that activated B cells are highly elevated in CRSwNP, and they may play an important role in the pathophysiology of disease. However, more studies are needed to determine the mechanisms by which B cells contribute to disease pathogenesis in CRSwNP.

Given that activated B cell subsets are highly elevated in CRSwNP, it is not surprising that several groups have reported elevated antibody levels of every isotype in nasal polyps as well [37, 39, 40]. In addition, it has been demonstrated that B cells in nasal polyps are activated locally to undergo class switch recombination, similar to what has been seen in allergic rhinitis [37, 39]. This suggests that the local inflammatory environment may play a key role in the development of potentially pathogenic antibody responses. While the specificity of these antibodies remains largely unknown, there is evidence that some of the IgE in nasal polyps is specific to proteins produced by *Staphylococcus aureus* and that some of the local IgG and IgA in nasal polyps are autoreactive [40–43]. Both of these types of antibodies could play very important roles in the inflammatory response that occurs in nasal polyps. In addition, recent work has identified elevated levels of activated

components of the classical, or antibody-mediated, complement pathway [44]. This provides further evidence to support the notion that antibody-mediated events may play a role in the inflammatory processes in CRSwNP.

While increased levels of IgE, IgA, IgM, and IgG antibodies are found in CRSwNP, increased levels of soluble IgD (sIgD), along with abundant IgD$^+$ plasmablasts, are found in nasal tissue in a subpopulation of CRS patients, more commonly among patients with CRSsNP [45]. Mucosal sIgD was associated with high local IL-2 levels and the presence of pathogenic bacteria in the sinonasal microenvironment. These findings suggest that IgD might contribute to enhancing protective mucosal immunity or, by contrast, represent a pathologic inflammatory response possibly driven by superantigenic effects. These investigations significantly advance our understanding of IgD and IgD-producing B cells in the setting of sinonasal inflammatory disease.

Targeting Treatment to Inflammatory Patterns in CRS

As presented above, it is evident that adaptive immune responses are upregulated in the mucosa of CRS patients, including local elevations of B and T cell subsets, and the antibodies and/or cytokines produced by these cells [33, 46]. In recent years, the repertoire of approved treatments for specifically targeting aspects of the adaptive immune system have dramatically increased. However, our persistent lack of understanding of the key inflammatory mechanisms driving CRS has limited the availability of these novel treatments for use in CRS. Thus, few of these targeted medications have been specifically studied in CRS, and none are currently approved for use in CRS. When considering targeting specific aspects of the adaptive immune response, it is also important to consider that the primary impairment suffered by patients with CRS is on their quality of life. Thus, while epidemiologic studies do associate CRS with incident lower airway disease and cerebrovascular events, the efficacy of novel targeted treatments for CRS has to be weighed against potential risks and costs of treatment.

To date, all published randomized controlled trials (RCTs) of targeted therapies in CRS have examined the efficacy of monoclonal antibodies targeting aspects of type 2 inflammation in CRSwNP patients (Table 1). In the first omalizumab (humanized anti-IgE) study, 14 patients (12/14 CRSwNP) were randomized to receive placebo or subcutaneous omalizumab every 4 weeks for 6 months [48]. Patients in this study had non-significant decreases in radiographic disease severity from 76.1 to 60% pre- to post-treatment. Similarly, none of the secondary outcomes, including nasal endoscopy scores, SNOT-20 scores,

olfactory testing, nasal peak inspiratory flow, or eosinophil levels in nasal lavage, were significantly different in the treatment group. In contrast, a separate study randomized 24 allergic and non-allergic patients with CRSwNP to receive 4–8 doses of subcutaneous omalizumab or placebo [47]. Patients in the treatment arm were noted to have significantly decreased endoscopic nasal polyp scores and Lund-Mackay CT scores, regardless of their atopic status. Patient reported measures including nasal and asthma QoL measures, and symptom questionnaires also demonstrated significant differences. The fact that this treatment was effective in both atopic and non-atopic patients suggests that omalizumab may have therapeutic benefits that are independent from decreasing IgE. The contrasting findings presented in these two studies may be due to differences in patient selection criteria, length of treatment, and/or timing of the measurements after the treatment.

Similarly, mixed results have been published for monoclonal antibodies targeting IL-5. A phase 1 study of 24 CRSwNP patients compared placebo to a single 1- or 3-mg/kg intravenous dose of reslizumab (humanized anti-IL-5) [49]. The study authors noted that the drug was well tolerated in patients but that there were no significant differences in nasal polyp size across treatment groups, although subgroup analysis demonstrated potentially increased efficacy among patients with high tissue levels of IL-5 [49]. A separate study examined 20 CRSwNP patients who were randomized to receive mepolizumab (anti-IL-5) or placebo [50]. This study found that 60% of the treated group, compared to 10% of the placebo group, had reductions in polyp size, postnasal drip, and improved olfaction. In addition, patients in the treated group had decreased blood eosinophil levels, ECP, and blood IL-5R expression at 8 weeks. Again, these studies suggest that there may be a benefit for treatment with anti-IL-5, at least in a subset of CRSwNP patients.

The most recent randomized trial examined the efficacy of dupilumab, a fully humanized antibody targeting the common alpha subunit of the IL-4 and IL-13 receptor. In this multicenter study, 60 CRSwNP patients were randomized to receive weekly dupilumab or placebo for 16 weeks [15]. Seventy percent of treated patients, compared to 20% in the placebo group, had polyp size reduction at 16 weeks. Significant improvements were also reported in Lund-Mackay CT scores, patient reported measures, and olfactory scores. Together these studies establish that type 2 inflammation, especially those mediated by IL-4 and IL-13, are likely to be pathogenic in patients with CRSwNP. Active ongoing and future clinical trials will help to better delineate the length of treatment and the patient subgroups most likely to benefit from these novel therapies.

Table 1 Randomized clinical trials of targeted therapies in CRS

Study Year [Ref]	Drug name/approved indication	Target	Study population	Reported treatment effects	Commonly reported symptoms	Comments
Gevaert P et al. 2013 [47]	Omalizumab/allergic asthma	IgE	CRSwNP with comorbid asthma ($n = 24$)	Reduction in: 1. Endoscopic nasal polyp scores 2. CT scores 3. Nasal and asthma symptom: nasal congestion, rhinorrhea, smell loss, and dyspnea 4. QoL questionnaires: physical health, sleep, and general rhinosinusitis outcome, asthma outcome. No significant change in: 1. Nasal and asthma symptom: cough 2. Spirometric results 3. QoL questionnaires: mental health 4. Serum and nasal secretion parameters	URI symptoms	1. Small sample size 2. Was effective independent of allergy status or elevated serum IgE
Pinto JM et al. 2010 [48]	Omalizumab/allergic asthma	IgE	CRSwNP ($n = 12$) and CRSsNP ($n = 2$)	Reduction in: 1. Radiographic severity. No significant change in: 1. SNOT-20 2. UPSIT 3. nPIF 4. Eosinophil levels	Concern for anaphylaxis, malignancy (1 patient)	1. Patient resumed previous therapy and have "rescue" medications
Gevaert P et al. 2006 [49]	Reslizumab/eosinophilic asthma	IL-5	CRSwNP: grade 3–4 or surgical salvage ($n = 24$)	Reduction in: 1. Endoscopic nasal polyp scores (qualitative) 2. Serum eosinophilia 3. IL-5 levels (serum and nasal secretion) 4. Soluble IL-5Rα (serum and nasal secretion) 5. ECP levels (serum and nasal secretion). No significant change in: 1. Symptoms: rhinorrhea, nasal obstruction, PND, smell loss 2. nPIF 3. Eotaxin levels (serum and nasal secretion)	URI symptoms	1. Increased baseline IL-5 levels (nasal secretion): predict responsiveness 2. Rebound eosinophilia at 24 weeks (1 mg/kg) and 32 weeks (3 mg/kg)
Gevaert P et al. 2011 [50]	Mepolizumab/eosinophilic asthma	IL-5	CRSwNP: grade 3–4 or surgical salvage ($n = 30$)	Reduction in: 1. Endoscopic nasal polyp scores 2. CT scores 3. nPIF 4. Symptoms: loss of smell, PND, congestion 5. Serum eosinophilia 6. IL-5Rα levels (serum and nasal secretion) 7. ECP levels (serum) 8. IL-6, IL-1β, and MPO levels (nasal secretion). No significant change in: 1. Symptom: rhinorrhea 2. ECP, IL-5, and total IgE (nasal secretion)	URI symptoms	1. Baseline IL-5 levels (nasal secretion): not predict responsiveness 2. Follow-up = 48 weeks

Table 1 (continued)

Study Year [Ref]	Drug name/approved indication	Target	Study population	Reported treatment effects	Commonly reported symptoms	Comments
Bachert C et al. 2016 [15]	Dupilumab/atopic dermatitis and asthma (pending)	IL-4Rα	CRSwNP with and without asthma (n = 60)	Reduction in: 1. Endoscopic nasal polyp scores 2. CT scores 3. nPIF 4. UPSIT 5. SNOT-22 6. Sinusitis symptom severity 7. IgE levels (serum) 8. Eotaxin-3 levels (plasma) 9. FEV1 (% predicted) and asthma QoL questionnaire (in patients with comorbid asthma) No significant change in: 1. Serum eosinophilia 2. Serum TARC levels	Nasopharyngitis, headache, injection site reactions	1. Effective blockade of both IL-4 and IL-13

CRSwNP chronic rhinosinusitis with nasal polyps, *CT* computed tomography, *QoL* quality of life, *URI* upper respiratory infection, *CRSsNP* chronic rhinosinusitis without nasal polyp, *SNOT-20* Sinonasal Outcome Test, *UPSIT* University of Pennsylvania Smell Identification Test, *nPIF* nasal peak inspiratory flow, *ECP* eosinophil cationic protein, *PND* postnasal drip, *TARC* thymus and activation-regulated chemokine

As discussed above, the proliferation of B cells and antibody production may have pathogenic consequences in CRSwNP. There is mounting evidence demonstrating the development of autoreactive B cell responses in nasal polyps and an increased activation of the classical complement pathway in nasal polyps [42–44, 51]. These findings suggest that the growing armamentarium of anti-B cell therapies used in treating autoimmune diseases may also be of therapeutic value in CRS, especially in patients with nasal polyps (Table 2). The best-characterized anti-B cell agent in clinical use has been rituximab (anti-CD20), which is indicated for use in rheumatoid arthritis and granulomatous polyangiitis [52]. However, rituximab use is also associated with increased rates of sinopulmonary infections, low, but concerning, rates of serious infections, and rarely progressive multifocal leukoencephalopathy. Unfortunately, this risk profile is likely unsuitable for treating a quality of life illness like CRS, and the potential for increased sinopulmonary infections is unlikely to be acceptable to CRS patients who already suffer an increased frequency of airway infections [53, 54]. Another drug, belimumab, targets the cytokine BAFF and has recently been approved for use in systemic lupus erythematosus. As discussed above, BAFF has previously been reported to be elevated in CRSwNP tissue, and its expression levels are correlated with increased local CD20 and IgA expression [34]. Importantly, safety studies of belimumab to date demonstrate comparable rates of sinopulmonary infections as placebo-treated groups [55]. Together, as increased experience with anti-B cell therapies is gained, safe options with potential efficacy in CRS may be identified for future study in CRS.

Conclusions

CRS is a complex and very heterogeneous disease, and it is becoming clear that defining patient subsets based solely on differences in clinical presentations may not be sufficient to adequately treat all patients. A better understanding the different inflammatory patterns within the tissue and sinuses of these patients may help to pave the way for new definitions of patient groups or endotypes. This information could then be used to more specifically target inflammatory pathways that contribute to disease pathogenesis. There are currently several different drugs that have been approved for the treatment of diseases other than CRS but which target specific aspects of the adaptive immune response that may contribute to CRS pathogenesis. Moving forward, new studies are needed to determine whether any of these available treatments could be beneficial to specific groups of CRS patients.

Table 2 FDA-approved drugs targeting B cell inflammation-related molecules

Drug name	Target	Approved indications	Known effects on airway	Other known major toxicity
Rituximab	mAb for CD20 (inhibits early-stage B lymphocyte activation)	Non-Hodgkin's lymphoma, chronic lymphocytic leukemia, rheumatoid arthritis, granulomatosis with polyangiitis (Wegener's granulomatosis) and microscopic polyangiitis	Upper and lower respiratory tract infection	Death, infusion reactions, severe skin and mouth reactions, HBV reactivation, progressive multifocal leukoencephalopathy
Ofatumumab	mAb for CD20 (inhibits early-stage B lymphocyte activation)	Chronic lymphocytic leukemia	Upper and lower respiratory tract infection, bronchitis, pneumonia, sinusitis, nasopharyngitis	Infusion reactions, HBV reactivation, HBV infection, progressive multifocal leukoencephalopathy, tumor lysis syndrome, cytopenias
Ocrelizumab	mAb for CD20 (inhibit early-stage B lymphocyte activation)	Multiple sclerosis	Upper and Lower respiratory tract infection	Infusion reactions, herpes virus-associated infections, progressive multifocal leukoencephalopathy, HBV reactivation, malignancy (including breast cancer)
Belimumab	mAb for BAFF (also known as BLyS)	Adult patients with active, autoantibody-positive, systemic lupus erythematosus Phase II clinical trials for rheumatoid arthritis and Sjogren's syndrome	Upper and lower respiratory tract infection, bronchitis, pneumonia, sinusitis, nasopharyngitis	Death, serious infections, malignancy (including non-melanoma skin cancer), anaphylaxis, infusion reactions, depression
Ibrutinib	Inhibitor of BTK	Mantle cell lymphoma, chronic lymphocytic leukemia	Upper respiratory tract infection, pneumonia, sinusitis, interstitial lung disease	Hemorrhage, infections, myelosuppression, renal toxicity, malignancy (including skin cancer), embryo-fetal toxicity
Trametinib	Inhibitor of MEK1 and MEK2	Unresectable metastatic melanoma with BRAF mutation	Interstitial pulmonary disease, pneumonitis	Cardiovascular (hypertension, cardiomyopathy, lymphedema), dermatologic (dermatitis acneiform, dry skin, pruritis, paronychia), gastrointestinal (diarrhea, stomatitis, abdominal pain), hematologic (anemia), Elevated ALT/AST
Bortezomib	Inhibitor of NF-κB	Multiple myeloma	Upper and lower respiratory infection, cough, dyspnea, nasopharyngitis, pneumonia, bronchitis, sinusitis	Peripheral neuropathy, myelosuppression (neutropenia, thrombocytopenia), gastrointestinal (asthenia)
Siltuximab	mAb for IL-6	Multicentric Castleman's disease	Upper respiratory infection	Peripheral edema, abdominal pain, pruritis, rash, increased weight
Tocilizumab	mAb for IL-6R	Rheumatoid arthritis, systemic juvenile idiopathic arthritis	Upper respiratory infection, nasopharyngitis	Elevated ALT and total cholesterol
Ruxolitinib	Inhibitor of JAK1 and JAK2	Intermediate or high-risk myelofibrosis (including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis)		Thrombocytopenia, anemia, neutropenia, herpes-associated infection, bruise, dizziness, headache, urinary tract infection, elevation of ALT/AST, hypercholesterolemia
Tofacitinib	Inhibitor of JAK3 and JAK1	Rheumatoid arthritis	Upper respiratory infection, nasopharyngitis	Infections, headache, diarrhea, hypertension, elevated ALT/AST, and serum creatinine

mAb monoclonal antibodies, *HBV* hepatitis B virus, *BAFF* B cell activating factor, *BLyS* B lymphocyte stimulator, *BKT* Bruton's tyrosine kinase, *MEK* mitogen-activated protein kinase kinase, *BRAF* B-Raf Proto-Oncogene, *ALT/AST* alanine aminotransferase/aspartate aminotransferase, *NF-κB* nuclear factor-κB, *JAK* janus kinase

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