

Research Article

Immunological background for treatments with biologicals in CRSwNP

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Abstract

Background: Chronic rhinosinusitis (CRS) is a heterogeneous and multifactorial inflammatory disease of the nasal and paranasal mucosa. To date, no internationally standardized uniform classification has been developed for this disease.

Usually, a phenotype classification according to CRS with (CRSwNP) and without (CRSsNP) polyposis is performed. However, through a variety of studies, it has been shown that even within these phenotypes, different endotypes of CRS exist, each with a different underlying inflammatory pathophysiology. In this mini-review, we aim to outline the essential immunological processes in CRSwNP and to highlight the modern therapeutic options with biologics derived from this disease.

Methods: Current knowledge on the immunological and molecular processes of CRS, especially CRSwNP, was compiled by means of a structured literature review. Medline, PubMed, national/international trial and guideline registries as well as the Cochrane Library were all searched.

Results: Based on the current literature, the different immunological processes involved in CRS and nasal polyps were elaborated. Current studies on the therapy of eosinophilic diseases such as asthma and polyposis are presented and their results discussed.

Conclusion: Understanding the immunological basis of CRSwNP may help to develop new personalized therapeutic approaches using biologics. Currently, 2 biologics (dupilumab, omalizumab) have been approved for the therapy of CRSwNP (polyposis nasi) in Europe.

Introduction

The prevalence of chronic rhinosinusitis (CRS) in developed countries is approximately 10% - 15% of the population, resulting in significant costs for healthcare systems and national economies [1,2].

The diagnosis of CRS has traditionally been based on clinical parameters. Here, the presence of 2 major symptoms (facial/head pressure, nasal obstruction, hyposmia/anosmia, or purulent nasal secretion) or one major symptom and at least 2 minor symptoms (headache, fever, halitosis, cough, toothache, fatigue, and ear pressure) over a period of more than 12 weeks is required [3]. In addition, current guidelines require endoscopic and/or radiologic evidence of inflammatory tissue in addition to 2 major criteria [1,3,4]. Phenotype classification is based on endoscopic examination

of the nasal cavity or imaging techniques. It divides CRS into chronic rhinosinusitis with nasal polyps (CRSwNP) and chronic rhinosinusitis without nasal polyps (CRSsNP).

However, CRSwNP and CRSsNP are not unitary syndromes because different pathomechanisms exist within these phenotypes, resulting in different forms of inflammation of the sinonasal mucosa. These are referred to as endotypes. In the future, this endotype classification could enable a targeted, pathophysiologically-based therapy for CRSwNP [5].

For this purpose, reliable and easy-to-determine biomarkers have to be developed [6].

Immunology of nasal polyps

CRSwNP is characterised, among other things, by a highly edematous stroma with subepithelial and perivascular

More Information

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Submitted: March 23, 2021

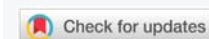
Approved: April 07, 2021

Published: April 08, 2021

How to cite this article: Klimek L, Hagemann J, Casper I, Huppertz T, Bedbrook A, et al. Immunological background for treatments with biologicals in CRSwNP. Arch Asthma Allergy Immunol. 2021; 5: 022-029.

DOI: 10.29328/journal.aaai.1001026

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infiltration of the inflammatory cells. Infiltration of activated T lymphocytes occurs in all subsets of paranasal sinus disease, but, in nasal polyps, different T lymphocyte subsets contribute [1]. In recent years, the T-cell subpopulations in chronic sinusitis and nasal polyposis have been well characterised, and their biological function determined.

In general, lymphocytes can be divided into a uniform B-lymphocyte population and various T-lymphocyte subsets. Divided into CD8 positive (CD8+) T suppressor cells and CD4+ T helper cells, CD4+ T cells are capable of differentiating into T helper (Th)1, Th2, Th9, Th17, Th22 and follicular T helper (Tfh) effector cells, among others [7,8]. The balance between these T-helper subtypes is extremely important for the physiology of the mucosal immune system and can be altered by persistent inflammatory processes. In CRSwNP, there is usually an eosinophilic, Th2-dominated cell infiltration [1]. Due to the mucosa of the upper and lower airways being permeable to various antigens (e.g., allergic antigens, bacterial antigens, nanoparticles) because of barrier disruption, epithelial cells are able to activate dendritic cells (DC) in the environment by producing thymic stromal lymphopoietin (TSLP). Interaction between the OX40 receptor (also known as CD134) on naïve T cells and the OX40 ligand on DCs induces CD4+ T cells to differentiate into Th2 cells [9,10]. The further inflammatory process is characterised by interleukin (IL)-4 and IL-5 production by these Th2 cells, as well as eosinophil cationic protein (ECP) and eotaxin-1/-2/-3 [11,12]. Each of these cytokines has specific functions. IL-4 is a mediator and modulator of the immune and inflammatory response and is mainly produced by Th2 cells. In addition, IL-4 is able to promote the differentiation of CD4+ T cells into Th2 cells, while inhibiting IFN γ production and Th1 response [13,14]. Recently, it has been shown that there is an upregulation of IL-4 in nasal polyps, whereas IFN γ is expressed in a decreased manner and does not differ significantly between nasal polyps and control tissues [12,15,16]. IL-5 is the major eosinophil-activating cytokine and promotes the tissue survival of mature eosinophils [17,18]. IL-5 is upregulated in nasal polyps [19] and plays an important role in their pathogenesis. ECP and eotaxin promote eosinophil attraction and activation, and are also upregulated in nasal polyps [11,12,20].

IL-6, as a proinflammatory cytokine, is capable of inhibiting neutrophil recruitment [21-23]. It has also been found to be upregulated in CRSwNP [24,25]. However, based on the different published data regarding regulatory molecules of the IL-6 pathway, it remains unclear as to whether the IL-6 pathway is a part of the pathogenesis of CRSwNP.

Keswani, et al. [26] and Cho, et al. [27] found increased expressions of IL-32 in total tissue extracts of nasal polyps. IL-32 is also described as a proinflammatory cytokine that induces cells of the immune system - such as monocytes and macrophages - to secrete inflammatory cytokines [28-33]. In this regard, IL-32 appears to play a role in various

inflammatory diseases such as chronic obstructive pulmonary disease (COPD) and atopic dermatitis [34,35]. There are now 9 different known isoforms of IL-32, although the functional differences remain unclear [29,36]. Further studies are needed to assess the role of IL-32 in the nasal polyps of patients with chronic rhinosinusitis.

IL-25 and IL-33 are other cytokines produced in sinonasal epithelial cells that support the Th2 inflammation of CRSwNP [37-39]. IL-25 is upregulated in nasal polyps and increases thymic stromal lymphopoietin (TSLP)-induced Th2 cell expansion [40,41]. TSLP has previously been shown to have increased expression in the epithelium of patients with CRSwNP [42-44]. This is an IL-7-like cytokine, and, in combination with IL-1, mast cells are effectively activated to produce Th2 cytokines, including IL-5 and IL-13 [45].

A study from Baltimore (US) could demonstrate that sinonasal epithelial cells from patients with untreated CRSwNP show an increased baseline expression of IL-33 compared to sinonasal epithelial cells from patients with CRSwNP after treatment with methylprednisolone [46]. This increased expression of IL-33 in untreated polyps was confirmed by another research group [47]. IL-33 is a local alarmin for various immune cells. In addition, IL-33 is a chemoattractant for Th2 cells and promotes the production of Th2 cytokines such as IL-4, IL-5 and IL-13. Airway epithelial cells can produce IL-33, and its receptor is expressed by eosinophils and Th2 lymphocytes, among others [48]. IL-33 plays a significant role in the maintenance of Th2-mediated eosinophilic inflammation [49], and polymorphisms within the IL-33 receptor gene - the interleukin-1 receptor-like 1 (IL1RL1) gene - have been linked to the severity of CRS [50]. IL-25 and IL-33 are thought to link epithelial cells to the Th2 response [37]; however, this requires further investigation.

On the other hand, the cytokines IL-25, IL-33, and TSLP have effects on the so-called type 2 innate lymphoid cells (ILC2) [51]. ILCs are lymphocyte-like cells that do not express allergen-specific T-cell receptors. In this regard, ILC2 cells are considered to be the counterpart of Th2 cells, as both produce cytokines such as IL-5 and IL-13 [52]. Thus, ILC2s activated by IL-33 and IL-25 can induce eosinophilic airway inflammation [53,54]. ILC2s are abundant in nasal polyps and are associated with (i) increased numbers of eosinophils in the blood and tissues of patients with CRSwNP, (ii) clinically relevant worsening of TNSS (Total Nasal Symptom Score) and (iii) asthma comorbidity [55,56].

In addition to eotaxin-1/-2/-3, several chemokines such as CCL5 (RANTES), CXCL8 (IL-8), CCL23, CCL18, CXCL12 (SDF-1 α), and CXCL13 (BCA-1) have been linked to the selective recruitment of inflammatory cells to mucosal tissue in CRSwNP. RANTES was one of the first identified chemokines to be found upregulated in nasal polyps [57,58]. RANTES is a member of the CC chemokine family and is a potent chemoattractant



for eosinophils and T lymphocytes, but not for neutrophils. It is primarily secreted by nasal epithelial cells [57,59,60]. Expression as well as secretion of RANTES also occurs in nasal polyps. Interestingly, nasal polyps with high numbers of eosinophils have a significantly increased RANTES gene and protein expression. Consequently, increased RANTES expression leads to increased numbers of eosinophils in the tissue. Thus, RANTES is also likely to play an important role in the mobilisation of eosinophils in nasal polyps.

Another role in the inflammation of nasal polyps is played by CXCL8 (IL-8), which attracts neutrophils and eosinophils to the nasal mucosa, provided they have been previously activated by IL-5 [61]. However, IL-8 is considered as rather a nonspecific marker for CRSwNP. While altered levels of IL-8 have been identified in nasal polyps [25,61-64], upregulation remains without clear correlation to nasal polyp formation [61].

Poposki, et al. [65] demonstrated a strong production of CCL23 in nasal polyps, which was largely colocalised with ECP, suggesting a predominant eosinophilic CCL23 production in nasal polyps. CCL23 is a chemoattractant for monocytes, dendritic cells and lymphocytes. It has been shown to induce endothelial cell migration via the chemokine receptor CCR1, which is also upregulated in nasal polyps [65-68]. Th2 cytokines such as IL-4 and IL-13 have been shown to induce CCL23 expression in monocytes [69].

Significantly increased CCL18 mRNA expression was also found in nasal polyps and inferior turbinates [70]. In CRSwNP, M2 macrophages and mast cells were identified to express CCL18, which can be induced by the Th2 cytokines IL-4, IL-13, and IL-10 [70]. Because the associated receptor CCR8 has only recently been identified, the role of CCL18 in the pathogenesis of CRSwNP has not yet been studied in detail [71]. However, this discovery will help clarify the role of CCL18 in CRSwNP.

B cells as well as IgA and IgE antibody fractions have been found to be elevated in patients with CRSwNP [72,73]. B cells express IgA, which triggers the degranulation of eosinophils and represents a possible link to CRSwNP [72]. In this context, the chemokines CXCL12 (SDF-1 α) and CXCL13 (BCA-1) have been shown to be increased in nasal polyps. Both of them attract B cells. Furthermore, the receptors for SDF-1 α (CXCR4 and CXCR7) and BCA-1 (CXCR5) are also present at elevated levels [74]. Accordingly, in nasal polyps, the expression of SDF-1 α and BCA-1 may be important for the recruitment and maintenance of B cells. In addition, the elevated IgA levels imply an important role of B cells in the pathogenesis of CRSwNP.

Clinical trials with biologicals in CRSwNP

Biologicals include therapeutics produced by biotechnological methods, particularly by the gene transfection of cells or other organisms. The most prominent

group of biologicals are monoclonal antibodies, which, in recent decades, have been increasingly used in so-called immunotherapy. Treatment of atopy, asthma, and other eosinophilic disorders with monoclonal therapeutic antibodies has increased dramatically in recent years [75-78]. For severe and refractory asthmatic syndromes, an antibody has already been approved for therapy, one that binds free IgE and reduces IgE receptor density on immune cells [79]. It is now undisputed that a large number of patients with CRSwNP also have comorbid bronchial asthma, and vice versa [80-82]. In particular, high levels of total IgE, ECP, and IgE against *S. aureus* are associated with lower and upper respiratory tract comorbidity and a high rate of polyposis recurrence after sinonasal surgery [81,83]. Based on this comorbidity, current and past studies have applied antibodies known in asthma therapy to CRSwNP, and have achieved significant success in some cases.

Further targets for therapy with biologicals

By studying nasal polyp tissue for the expression of inflammatory mediators and cellular markers, new potential targets for targeted therapy with biologicals in CRSwNP are continuously being identified. The same is true regarding experience in asthma therapy, of which the applicability to chronic sinusitis is being reviewed. Kimura, et al., Liu, et al. and other groups demonstrated increased concentrations of thymic stromal lymphopoietin (TSLP) in the polyp tissue of patients with CRSwNP [42-44]. Among these, the concentration was highest in allergic rhinitis with polyposis. Tissue dendritic cells (DC), which were also examined, showed an increased expression of the TSLP receptor and OX40 ligand (OX40L) compared with tissue from healthy subjects [43]. Anti-TSLP and anti-OX40L antibodies have already been studied in the context of asthma in clinical trials. They were able to reduce eosinophils in sputum, while anti-TSLP antibodies were also able to reduce eosinophils in blood [75,126]. The results of further studies with anti-TSLP antibodies are currently pending [127,128]. At the present time, there are no known clinical trials investigating TSLP or OX40L blockade in CRSwNP.

In 2013 and 2014, a phase I trial of a monoclonal therapeutic antibody against IL1RL1 was initiated in patients with CRSwNP and asthma, respectively [129,130]. AMG282 prevents the binding of IL-33 (whose key role has been described above) to its receptor IL1RL1. Results of these safety, tolerability, and pharmacokinetics studies are currently pending, and other IL1RL1 antibodies from other pharmaceutical companies, such as CNTO7160, are in preclinical and clinical development. A phase II trial investigating AK001- currently reported as being a SIGLEC8 ligand or antibody - in the treatment of CRSwNP is not presently in the recruitment phase [131,132]. SIGLEC8 is expressed on eosinophils, mast cells, and basophils, and binding of a SIGLEC8 ligand induces apoptosis in eosinophils [133]. This proapoptotic effect appears to be further



modulated by the presence of IL-33 and IL-5 [134,135]. The primary endpoints of the study were reduction in polyp size and CT polyp score (Lund-Mackay).

Studies investigating the effect of blockade of IL-2, tumour necrosis-factor-alpha (TNF α), and other cytokines and chemokines have been conducted only for asthma or atopic eczema indications, but not for CRSwNP. TNF α blockade, which has been well studied in rheumatoid disease and inflammatory bowel disease, has led to equivocal results and tolerability issues in asthma [136,137]. A phase II study of the treatment of asthma with daclizumab, an IL-2 receptor alpha antibody already approved to prevent rejection after kidney transplantation, showed promising results in terms of reduction of blood eosinophilia, ECP levels, asthma symptoms, and use of beta-mimetics as on-demand medication [138]. To date, this is the only study on daclizumab in asthma. Studies for the indication of CRSwNP have not yet been announced.

Conclusion

CRS is a heterogeneous group of inflammatory diseases of the mucous membranes of the nose and paranasal sinuses. In clinical routine, the disease is currently still divided into CRSsNP and CRSwNP based on phenological features.

However, especially for CRSwNP, different pathomechanisms exist that lead to the expression of the polyps. These different endotypes exhibit differential signalling pathways from the process of inflammation initiation, maintenance, and chronification to tissue alteration. In addition to the "classic" CRSwNP endotype of Th2-based and eosinophil-dominated inflammation, other endotypes exist that suggest different therapeutic approaches [139]. Examples include the use of biologics such as dupilumab (anti-IL-4/13), mepolizumab (anti-IL-5), or omalizumab (anti-IgE) [140,141].

These endotype-based treatment approaches target a specific pathophysiological pathway and are thus based on a careful selection of the patient population. Under these conditions, positive treatment success in CRSwNP has been demonstrated for the above-mentioned monoclonal antibodies against IgE, IL-5, and IL-4/13 [139].

However, the addition of individualised treatment options to "basic therapy options" could help to realise the principle of "personalised medicine", also for CRS in the future. Easily determinable biomarkers ([13,30] and clinical documentation parameters [142] are needed to establish these options in clinical routine, and their development is currently being pursued.

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