

## REVIEW ARTICLE

# IL-4/IL-13 pathway in nasal type 2 inflammation: The central role and targeted therapy

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## Funding information

National Key Research and Development Program of China, Grant/Award Number: 2022YFC2504100; National Natural Science Foundation of China, Grant/Award Numbers: 82171109, 82025010

## Abstract

Type 2 dominant inflammation in nasal mucosa is the key underlying pathophysiological mechanism of allergic rhinitis (AR) and most presentations of chronic rhinosinusitis with nasal polyps (CRSwNP). Interleukin-4 (IL-4) and IL-13 share common receptor subunits and signaling molecules, which lead to various pathological changes in different cells, playing key roles in the pathogenesis of nasal type 2 inflammation. Numerous clinical trials have shown that biologics targeting key molecules of the IL-4/IL-13 pathway, especially IL-4 receptor alpha, can treat CRSwNP and AR with high efficacy, and are generally well tolerated. Several biologics have been approved for the treatment of difficult-to-control CRSwNP, while others also show promising results. Here, we review the IL-4/IL-13 pathway, its role in nasal type 2 inflammation, and current targeted therapies related to the IL-4/IL-13 pathway, with a focus on AR and CRSwNP.

## KEYWORDS

biologic, IL-13, IL-4, nasal type 2 inflammation

## INTRODUCTION

Allergic rhinitis (AR) is a common allergic disorder characterized by inflammation of the nasal mucosa in response to allergens and affects up to 40% of the general population worldwide [1, 2]. Chronic rhinosinusitis with nasal polyps (CRSwNP), with a prevalence of 1.1%–4.3% worldwide, is a chronic inflammatory condition that involves persistent inflammation of the sinus mucosa and the growth of polyps (benign growths) in the nasal cavity [3–5]. The typical symptoms of AR include rhinorrhea, sneezing, nasal blockage, and/or itching of the nose [6], while patients with CRSwNP report the presence of rhinorrhea, nasal congestion, hyposmia and facial pain that lasts for more than 12 weeks [7]. Type 2 dominant

inflammation of the nasal mucosa is the key underlying pathophysiological mechanism of AR and most presentations of CRSwNP, which are widely regarded as nasal type 2 inflammation. This immune response is characterized by high infiltration of eosinophils, basophils, mast cells, and other inflammatory cells, as well as the robust expression of cytokines, including interleukins (IL)-4, IL-5, and IL-13 [8, 9]. Recently, targeted strategies, especially biologics aimed to suppress key pathogenic pathways of type 2 inflammatory response, have been proven effective in relieving the symptoms of AR and CRSwNP. Here, we review the IL-4/IL-13 pathway and its role in nasal type 2 inflammation, as well as current targeted therapies relating to the IL-4/IL-13 pathway, with a focus on AR and CRSwNP.

Zhiqiu Zhu and Chaoran Zhao contributed equally to this study.

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## EXCESSIVE TYPE 2 INFLAMMATORY RESPONSE IN AR AND CRSwNP

The nasal epithelium is the first defense line in the upper airway, which mainly consists of ciliated cells, goblet cells, and basal cells, playing critical roles in mucociliary clearance and host defense [10, 11]. Allergens, pathogenic microorganisms, and other environmental factors interact with epithelial cells and trigger the release of alarmin cytokines IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) to initiate and amplify type 2 inflammatory responses [12, 13]. These alarmins act on various immune cells including T cells, B cells, dendritic cells (DCs) and mast cells, promoting the production of type 2 cytokines IL-4, IL-5, and IL-13. Type 2 cytokines contribute to the recruitment and activation of eosinophils, mast cells, basophils, and type 2 helper T (Th2) cells, ultimately promoting type 2 inflammation and tissue damage [14, 15].

The cells and group 2 innate lymphoid cells (ILC2s) are crucial in the pathogenetic process of nasal type 2 inflammation, and it is well known that the frequency of these cells elevates significantly in the peripheral blood of patients with AR and CRSwNP [16–18]. Alarmins, mainly derived from epithelial cells during the inflammation, promote the differentiation of naive CD4-positive T cells into Th2 cells and activate ILC2s [19, 20]. The activated Th2 cells and ILC2s recruit and activate basophils, mast cells and eosinophils by secreting IL-4, IL-5, and IL-13 [21, 22]. IL-5 induces the maturation of eosinophils and the release of toxic granules to cause tissue damage and inflammation, leading to tissue remodeling and exacerbating nasal pathology [23, 24]. Several studies have demonstrated that intravenous administration of a humanized anti-human IL-5 monoclonal antibody reduced the size of nasal polyps [25, 26]. IL-4 determines the polarization of CD4 cells to effector Th2 cells and is an essential factor for immunoglobulin E (IgE) production [27–29]. IL-13 is found to be associated with mucous gland hyperplasia and epithelial remodeling [30, 31]. In nasal polyps characterized by the tissue expression of IL-5, IL-4, and IL-13, these cytokines orchestrate the secretion of mucin 5AC (MUC5AC) and MUC5B [32, 33]. Type 2 cytokines, particularly IL-4, could downregulate the expression and distribution of tight junction proteins, such as occludins and zonula occludens, thus leading to damaged epithelial barrier in AR and CRSwNP [34, 35]. In addition, Th2 cytokines are involved in the damage of human nasal mucociliary differentiation and ciliary beat frequency in patients with CRSwNP [36, 37].

However, the development of nasal type 2 inflammation in AR and CRSwNP also involves different molecular mechanisms. For example, allergen and allergen-specific IgE play a central role in the development of AR rather than CRSwNP. IgE molecules are released by plasma cells and bound to high-affinity receptors on the surface of mast cells and basophils after sensitized individuals are exposed to allergens. They then cause degranulation and release of inflammatory mediators (histamine, tryptase, prostaglandins and leukotrienes), leading to sneezing and rhinorrhea of the upper respiratory tract [38, 39]. However, other environmental exposures, such as *Staphylococcus aureus*, can interact with epithelial cells and induce epithelial

cell-derived IL-33 and TSLP, thereby initiating type 2 immune response and propagating type 2 cytokine expression [40].

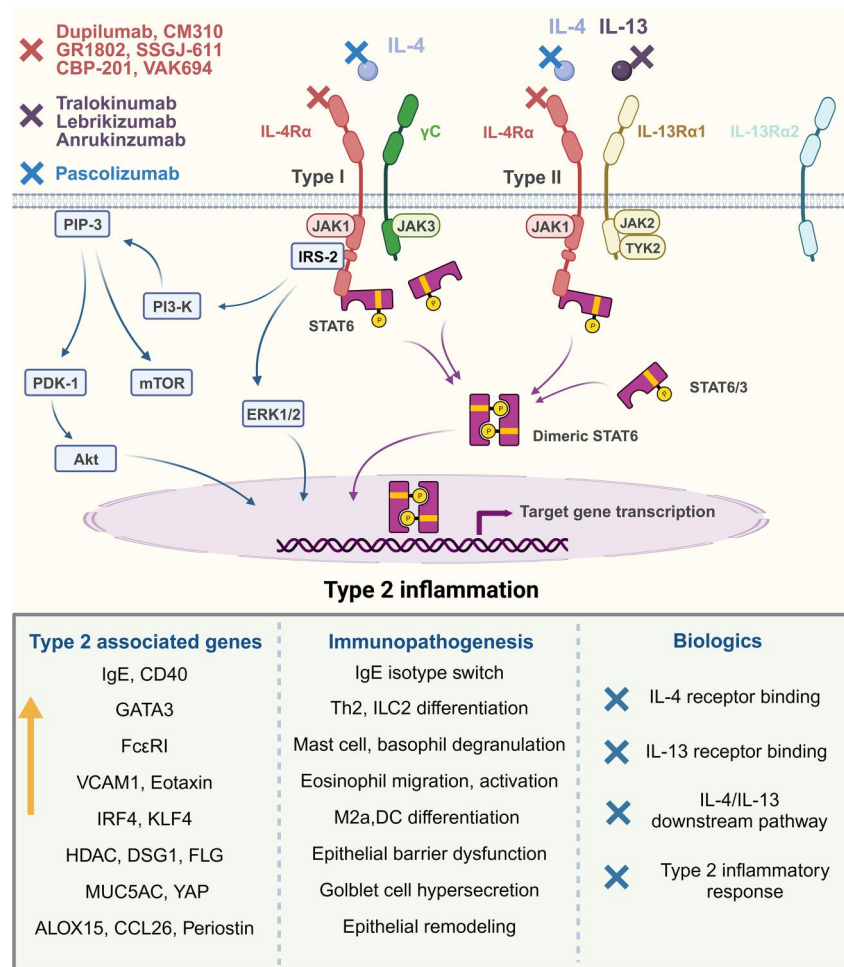
## IL-4 AND IL-13 SIGNALING PATHWAY

The genes of IL-4 and IL-13 are adjacent to each other in a 3000 kb gene cluster on chromosome 5 and share cis- and trans-regulatory elements [41]. When hosts are stimulated by allergens, pathogens and tissue damage, IL-4 and IL-13 are produced by immune cells, such as Th2 cells, mast cells, eosinophils and basophils [42, 43]. The level of IL-4 and IL-13 strongly implicate the development and progression of type 2 inflammation [44, 45].

IL-4 and IL-13 interact with their receptors to exert biological functions (Figure 1). IL-4 can act on two types of receptors to signal downstream, which are referred to as type I receptor, consisting IL-4R $\alpha$  and  $\gamma$ C receptor subunits, and type II receptor, consisting IL-4R $\alpha$  and IL-13R $\alpha$ 1 subunits that also serve as the receptor for IL-13 [46, 47]. Thus, IL-4 and IL-13 share common signaling pathways in cells that express type II receptor [48]. The differential expression of  $\gamma$ C and IL-13R $\alpha$ 1 determines whether IL-4 will signal via type I or type II receptor [42]. Additionally, IL-13 can interact with IL-13R $\alpha$ 2, which also functions as a decoy receptor since IL-13R $\alpha$ 2 has a short intracellular domain and lacks a signaling kinase [49, 50].

Upon binding to type I receptor, IL-4 forms a stable receptor complex with  $\gamma$ C, which phosphorylates and activates janus tyrosine kinase 1 (JAK1) and JAK3 [51, 52]. Activated JAKs promote the phosphorylation of tyrosine residues in the cytoplasmic tail of IL-4R $\alpha$ . The phosphorylated tyrosine residues serve as a docking site for signal transducer and activator of transcription 6 (STAT6) [44], which subsequently go through dimerization and translocates to the nucleus, where it activates the expression of various IL-4 responsive genes [48]. In addition, the pY497 residue forms an IL-4 and the insulin receptor like motif that interacts with the phosphotyrosine binding domain on insulin receptor substrate-2 (IRS-2) [53, 54]. Phosphorylated IRS-2 binds and activates the p85 structural domain of phosphoinositide 3-kinase (PI3K), which further activates phosphatidylinositol-3-phosphate (PIP3) [55]. This interaction of IL-4 and type I receptor is essential for Th2 cell response, and the activation of eosinophil and macrophage. Particularly, PIP3 activates pyruvate dehydrogenase kinase 1 and the mechanistic target of rapamycin C2 (mTORC2), thereby phosphorylating protein kinase B (AKT) and serine/threonine-protein kinase 1 (SGK1) on serine 473, ultimately leading to Th2 polarization [56].

Similarly, when IL-4 and/or IL-13 interact with type II receptors, the activation of either JAK1 or JAK2, in turn, activates the STAT6 signaling pathway [57, 58]. On the other hand, the Box1 region and c-terminal tail of IL-13R $\alpha$ 1 binds to tyrosine kinase 2 (Tyk2) and induces the phosphorylation of Tyk2, which, in turn, phosphorylates STAT3, induces its dimerization and nuclear translocation, and initiates gene transcription. IL-4 and IL-13 may compete for ligand-binding subunits in cells expressing type II receptors, since the binding affinity of IL-4 for IL-4R $\alpha$  is significantly higher than that of



**FIGURE 1** Immunopathogenesis of IL-4/IL-13 signaling pathways and targeted biologics. The binding of IL-4 and/or IL-13 with type I or type II receptor, leads to activation of intracellular signaling molecules such as STAT6 and IRS-2, followed by activation of target gene transcription. IL-4 and IL-13 receptors are widely expressed on most cell types, which leads to various pathological changes in different cells, contributing to the pathogenesis of type 2 inflammation. ALOX15, arachidonate 15-lipoxygenase; CCL26, C-C Motif Chemokine Ligand 26; DSG1, desmoglein 1; ERK1/2, extracellular signal-regulated kinase 1/2; FLG, filaggrin; HDAC, histone deacetylase; IRF4, interferon regulatory factor 4; IRS-2, insulin receptor substrate 2; JAK, janus tyrosine kinases; KLF4, krueppel-like factor 4; mTOR, mechanistic target of rapamycin; MUC5AC, mucin 5AC; PDK, pyruvate dehydrogenase kinase; PI3K, phosphoinositide 3-kinase; PIP-3, phosphatidylinositol-3-phosphate; STAT6, signal transducer and activator of transcription 6; Tyk, tyrosine kinase; VCAM, vascular cell adhesion molecule; YAP, yes associated transcriptional regulator. Figure was created with [BioRender.com](https://www.bio-render.com/).

IL-13 for IL-13Rα1 [59, 60]. Thus, in nonhematopoietic cells, the concentrations of IL-4 and IL-13 in the extracellular environment are important determinants of type II receptor signaling [56, 61]. No matter which molecule dominates the binding, type II receptors are essential for allergen-induced airway hyperresponsiveness and mucus hypersecretion. IL-4 and IL-13 promote arachidonate 15 lipoxygenase (ALOX15) expression via Jak2/Tyk-STAT6, whose expression product leads to the activation of the mitogen-activated protein kinase-extracellular signal-regulated kinase pathway, causing eosinophilic inflammation [62]. Meanwhile, IL-13 activates activator protein 1 (AP-1) through the extracellular signal-regulated kinase 1/2 (ERK1/2) signaling pathway, thus inducing the production of MUC5AC and MUC5B [63, 64].

## IL-4/IL-13 PATHWAY IN NASAL TYPE 2 INFLAMMATION

In the upper airway, a variety of cells including immune cells, epithelial cells, and structural cells, express IL-4 and IL-13 receptors, are regulated by IL-4/IL-13 signaling and are involved in the pathogenesis of airway type 2 inflammation. When IL-4 and IL-13 interact with their receptor, the latter alters its conformation and mediates different intracellular signaling pathways depending on the type of cells [65, 66]. IL-4 gives priority to activating Th2 cells, macrophages, and fibroblasts, while IL-13 gives priority to regulating smooth muscle contraction, goblet cell proliferation, and mucus secretion [67, 68]. In AR and CRSwNP, IL-4/IL-13 signaling is associated with

IgE isotype switching, Th2 cell differentiation, driving the migration of inflammatory cells to local inflammation sites, the release of proinflammatory cytokines, disruption of the epithelial barrier and tissue remodeling [69, 70].

## Lymphocytes

As the target cells of the IL-4/IL-13 pathway, lymphocytes such as T cells and B cells play important roles in triggering and maintaining nasal type 2 inflammation (Figure 1). The IRS-2/mTORC2 pathway activated by IL-4 and its regulation on downstream GATA3 and STAT6 are two keys for regulating the differentiation of naive T cells to Th2 cells [27, 66]. Additionally, the IRS-2/mTORC2 pathway also promotes the differentiation of Treg cells into Th2-like cells [51]. Activated Th2 cells secrete several key cytokines of type 2 inflammation, including IL-4, IL-13, IL-5, and IL-9, which affect eosinophil and mast cell recruitment, as well as stimulate B cell activity. Both IL-4 and IL-13 are involved in IgE class switching, which promotes IgE synthesis. IL-4 signaling also results in the binding of STAT6 to the IL-4-responsive element of the epsilon gene promoter, in synergy with CD40 engagement from T cells, leading to the transcription of IgE locus and driving IgE class switching [46, 71]. IL-13 also promotes IgE expression through STAT6 and upregulates the CD40 receptor on the surface of B cells. In addition, IL-4 induces the expression of major histocompatibility complex class (MHC) II molecules CD80, CD86, CD40, and surface IgM to enhance the antigen-presenting ability of B cells [70].

## Innate immune cells

The binding of IgE and its receptor FcεRI on the surface of mast cells and basophils leads to the release of large amounts of cytokines and chemokines, such as histamine, leukotriene, prostaglandin G2 and anaphylactic slow-reacting substances, contributing to the onset of type 2 inflammation [72, 73]. IL-4 has been proven to enhance the expression of FcεRI in mast cells and basophils through the STAT6 pathway [74]. Moreover, IL-4 plays a role in regulating chemokine secretion in mast cells, basophils, and eosinophils [75]. IL-4 also promotes the migration of eosinophils by interacting with the vascular cell adhesion molecule-1 and stimulating the release of eotaxin [76]. Similarly, IL-13 has been implicated in promoting eosinophil survival, activation, and recruitment [77].

In macrophages, IL-4 activates PI3K-AKT-mTORC2 and STAT6 pathways, both of which promote M2 macrophage polarization through upregulation of transcription factor interferon regulatory factor 4 [78, 79]. Thereafter, M2 macrophages reduce fibrin degradation, and induce tissue remodeling and nasal polyp formation. Studies have found that coagulation factor XIII in polyp tissue is mainly produced by M2 macrophages, and IL-13 inhibits the expression of tissue plasminogen activator, which leads to substantial

deposition of nasal mucosal fibrin [73, 80]. M2a macrophage also releases IL-10, CCL22, and CCL17, which promote the infiltration of Th2 cells. The combination of IL-10 and IL-4 enhances the expression of M2a-related genes in bone marrow-derived macrophages, and increases eosinophil migration [81]. Additionally, IL-13 stimulates the expression of low-affinity IgE receptors CD23, MHC-II, and phagocytic mannose receptors in monocytes of patients with asthma, thereby facilitating inflammatory responses [82].

DCs are overactivated in allergic diseases, resulting in the activation and proliferation of Th2 cells. IL-13 signaling is required for DC differentiation and migration to the draining lymph nodes to induce Th2 cell polarization. Recently, a migratory DC2 population with low CD11b expression unique to the dermis has been discovered. Its differentiation depends on krueppel-like factor 4 and STAT6 downstream of IL-13 signaling. ILC2-derived IL-13 controls the ability of DC2s to prime Th2 cells [83].

## Epithelial cells

Studies have shown that IL-4 and IL-13 cause epithelial remodeling and disruption of the epithelial barrier. IL-4 elevates Trex1 level to upregulate histone deacetylase, which leads to epithelial barrier dysfunction by downregulating tight junction protein expression [84]. Antagonizing IL-4 prevented mucosal barrier disruption and tight junction downregulation in a mouse model of house dust mite allergic airway inflammation [85]. IL-13 treatment significantly induced epithelial barrier dysfunction through decreased expression of the tight junction proteins desmoglein 1 and flaggrin. Interestingly, butyrate and propionate could restore this process in cultured human esophageal epithelial cells [86]. Moreover, IL-13 was able to induce yes-associated transcriptional regulator activity, leading to the proliferation and differentiation of goblet cells [87]. IL-13 upregulates the expression of AP1 and MUC5AC through ERK1/2 signaling, thereby stimulating goblet cells to secrete mucus. In addition, IL-4 and IL-13 can induce the expression of ALOX15 by activating the Jak2-Tyk2/STAT6 pathway. ALOX15 generates 15-HETE, inducing the expression of CCL26, MUC5AC, and periostin, the migration of immune cells such as eosinophils and DCs, as well as the differentiation of goblet cells [62].

## BIOLOGICS TARGETED IL-4/IL-13 PATHWAY

Biologics are a kind of biological response modifiers that interact with targets in a highly specific manner. For example, Secukinumab (AIN457), a monoclonal antibody targeting IL-17a, has been widely used in the treatment of psoriasis [88]. Since the IL-4/IL-13 pathway plays a crucial role in the initiation and exacerbation of type 2 inflammation, a large number of biologics targeting key molecules of the IL-4/IL-13 pathway, such as IL-4Rα, IL-4, and IL-13, have been developed by various pharmaceutical companies. Clinical trials have been conducted to investigate the safety and efficacy of these

biologics in treating type 2 inflammation. Clinical data from biologics anti-IL-4 (altrakincept and pascolizumab) and anti-IL-13 (anrukinzumab, tralokinumab, lebrikizumab, and dectrekumab) have been modest. Selection of an appropriate IL-4 or IL-13 epitope may be paramount in demonstrating the effects of IL-4 or IL-13 neutralization [89] (Table 1). Currently, IL-4R $\alpha$  is the most common target used to block IL-4/IL-13 signaling. Promisingly, biologics targeting IL-4R $\alpha$ , such as Dupilumab, CM310, and CBP210, have shown obvious clinical value in the treatment of airway type 2 inflammation (Table 1). When monoclonal antibody competitively binds to IL-4R $\alpha$ , IL-4/IL-13 signaling pathways are both suppressed due to: (1) inhibiting the binding of IL-4 to type I receptor complex; (2) inhibiting the assembly of type II receptor complex by preventing the recruitment of the IL-4R $\alpha$  subunit after IL-13R $\alpha$ 1 binding to IL-13 [51]. Accordingly, biologics targeting IL-4R $\alpha$  serve as negative regulators of IL-4/IL-13 downstream pathways such as STAT6 and IRS-2, thereby inhibiting IgE isotype switching in B cells and restraining Th2 inflammatory responses [46].

## Dupilumab

Dupilumab is a humanized IgG4 monoclonal antibody that targets the IL-4R $\alpha$  chain, which has been officially approved for several type 2 inflammatory diseases, including moderate to severe atopic dermatitis (AD) [90–92], moderate-to-severe eosinophilic or oral steroid-dependent asthma [93, 94], inadequately controlled CRSwNP [95, 96] and aspirin-exacerbated respiratory disease [97, 98]. Since the first proof-of-concept study of dupilumab was reported in 2016, 25 clinical trials have been conducted on CRSwNP worldwide, which have demonstrated broad efficacy in CRSwNP

management [99]. In the phase III SINUS 24-week and 52-week trials in adults with severe CRSwNP, dupilumab added to the standard of care significantly reduced polyp size, sinus opacification and severity of symptoms versus placebo, and was generally well tolerated [7, 100–102]. One clinical study conducted in the Asian population proved that long-term use of dupilumab (more than 4 years) had a satisfying effect, with significant improvement in subjective symptoms and no recurrence or significant side effects [103]. Loss or reduction in the sense of smell is one of the most troublesome and difficult-to-treat symptoms of CRSwNP. It has been proved that dupilumab provided rapid and lasting improvements in the sense of smell in patients with severe CRSwNP, regardless of prior sinonasal surgery, corticosteroid use or the presence of asthma [101, 104]. The use of dupilumab in patients with asthma and CRSwNP was overall associated with significant improvements in lung function, asthma control rates, and quality of life [7, 105].

A large number of clinical trials have also been conducted to evaluate the efficacy of dupilumab in the treatment of moderate to severe AR [106]. In two phase III trials of asthma with persistent AR, dupilumab significantly improved the SNOT-22 score, major AR symptoms, lung function, severity of asthma and rates of exacerbation [106, 107]. Campion *et al.* showed a strong effect of dupilumab on reducing allergen-specific IgE levels in sensitized patients, not only in serum but also in the nasal mucosal lining fluid, supporting the hypothesis that blockage of IL-4/IL-13 signaling leads to reduced IgE production and amelioration of allergic symptoms in sensitized patients [108]. Recently, dupilumab has been used in combination with subcutaneous immunotherapy (SCIT) to treat patients with seasonal AR, which showed that 16 weeks of SCIT + dupilumab may improve SCIT tolerability [109, 110]. All the above evidence demonstrates the

**TABLE 1** Biologics targeting IL-4/IL-13 pathway related to the treatment of type 2 inflammation.

Biologics	Targets	Indications (type 2 inflammatory diseases; current status)
Dupilumab	IL-4R $\alpha$	Moderate-to-severe AD (approved) [116]; uncontrolled CRSwNP (approved) [117]; EoE (approved) [118]; moderate-to-severe eosinophilic or oral steroid dependent Asthma (approved) [119]; AERD (approved) [120]; AFRS (phase III); AKC (phase II); ABPA (phase II); AR (phase II) [109]
CM310	IL-4R $\alpha$	Asthma (phase III); AR (phase III); CRSwNP (phase III) [113]; AD (phase III)
GR1802	IL-4R $\alpha$	CRSwNP (phase II); AD (phase II); asthma (phase II)
SSGJ-611	IL-4R $\alpha$	CRSwNP (phase II); AD (phase II)
CBP201	IL-4R $\alpha$	AD (phase III); asthma (phase II) [121]; CRSwNP (phase II)
Tralokinumab	IL-13	Moderate-to-severe AD (approved) [122]; asthma (phase III; terminated due to presenting inconsistent effect) [123]
Lebrikizumab	IL-13	Moderate-to-severe AD (approved) [124]; asthma (phase III; terminated due to presenting inconsistent effect) [125]
Anrukinzumab	IL-13	Asthma (phase II; terminated due to lack of efficacy)
VAK694	IL-4	AR (phase II; terminated due to no additional benefit) [126]
Pascolizumab	IL-4	Asthma (phase II; terminated due to no significant reduction in serum IgE) [127]

Abbreviations: ABPA, allergic bronchopulmonary aspergillosis; AD, atopic dermatitis; AERD, aspirin exacerbated respiratory disease; AFRS, allergic fungal rhinosinusitis; AKC, atopic keratoconjunctivitis; EoE, eosinophilic esophagitis.

promising effectiveness of dupilumab in the treatment of nasal type 2 inflammatory diseases.

## CM310

CM310 is a humanized monoclonal antibody that specifically binds to IL-4R $\alpha$ , preventing its interaction with IL-4 and IL-13. The epitope of CM310 to IL-4R $\alpha$  differs from that of dupilumab, as evidenced by the differential cross-species reactivity of CM310 binding to humans, rats and cynomolgus monkeys, whereas dupilumab binds only to human IL-4R $\alpha$ . This divergence indicates distinct mechanisms in precluding IL-4R $\alpha$  signaling and leads to different clinical outcomes. In an ovalbumin-induced rat experimental allergic conjunctivitis model, CM310 alleviated the conjunctival symptoms, decreased serum IgE, and suppressed infiltration of eosinophils and mast cell degranulation [111]. As an investigational monoclonal antibody, the safety and efficacy of CM310 have been demonstrated in healthy volunteers and type 2-related AD (NCT04893941; NCT04805411). Over a 16-week treatment period, both CM310 regimens (150 and 300 mg every 2 weeks) produced marked improvements in AD clinical manifestations, including pruritus, skin lesions, and quality of life [112]. Furthermore, in a multicentre phase II clinical trial on adult patients with severe eosinophilic CRSwNP, CM310 provided rapid and significant improvements regarding all aspects of the disease, involving polyp size, sinus opacification, the severity of symptoms, quality of life, as well as considerable reductions in type 2-related biomarkers and tissue eosinophils [113]. The long-term efficacy and safety of CM310 during or more than 24 weeks are being evaluated in the ongoing phase III clinical study (NCT05436275) with a larger sample size.

## Other biologics targeting IL-4R $\alpha$

In addition to dupilumab and CM310, several biologics targeting IL-4R $\alpha$ , including CBP201, GR1802, and SSGJ-611, are undergoing evaluation in phase II clinical trials for the treatment of type 2 inflammatory diseases. Preclinical studies on the immunological characterization of CBP-201 (rademikibart) showed that CBP-201 inhibited IL-4 and IL-13-mediated STAT6 signaling, TF-1 cell proliferation, and TARC production in PBMCs. Interestingly, CBP-201 rapidly downregulated IL-4, IL-13 and TARC gene expression in Th2-stimulated human skin explants, even with greater effectiveness than dupilumab for IL-4 [114]. Very recently, phase I randomized trials of CBP-201 in healthy individuals and patients with AD showed that CBP-201 is well-tolerated, with no serious treatment-emergent adverse events. CBP-201 treatment was associated with rapid and sustained improvements in eczematous lesions, pruritus, quality of life and inflammatory biomarker concentrations during 4 weeks of treatment. These efficacy responses did not plateau during the 4-week treatment and were generally dose-dependent [115].

Therefore, these medications also show promise for the treatment of type 2 inflammation.

## CONCLUSION

The emergence of biologic therapies for the treatment of nasal type 2 inflammation has shown promising effects. Several biologics have been approved for CRSwNP, including dupilumab (anti-IL-4R $\alpha$  monoclonal antibody) for difficult-to-control CRSwNP, mepolizumab (anti-IL-5 monoclonal antibody) for refractory severe CRSwNP, and omalizumab (anti-IgE monoclonal antibody) for adult refractory CRSwNP [26, 128–130]. Currently, regarding the treatment of AR, only omalizumab has been approved for the treatment of severe pollinosis in Japan [131]. Based on a large number of ongoing clinical trials and their promising results, more biologics are likely to be approved for the treatment of CRSwNP and AR.

Due to the central role of the IL-4/IL-13 pathway in type 2 inflammation, many biologics targeting IL-4R $\alpha$  have been developed and shown obvious efficacy in reducing nasal symptoms, improving quality of life and reducing the need for systemic corticosteroids in patients with nasal type 2 inflammation. However, several key issues need to be noted. Firstly, due to disease heterogeneity, not all patients with CRSwNP or AR are suitable for biologics. Clinical trials of dupilumab and CM310 indicated 21%–35% of the CRSwNP patients are not responsive (non-responders) to anti-IL-4R $\alpha$  treatment [7, 113]. Therefore, it would be important to investigate biomarkers to distinguish between responders and non-responders, together with patient clinical traits. Secondly, limited data are available regarding the treatment duration, long-term safety, and therapeutic effects of biologics. Furthermore, new topical formulations for biologics such as nasal spray or atomization, that directly target nasal mucosa, may have potential clinical implications for patients with nasal type 2 inflammatory diseases without complications.

## AUTHOR CONTRIBUTIONS

**Zhiqiu Zhu:** Writing—original draft (equal). **Chaoran Zhao:** Writing—original draft (equal). **Ming Wang:** Writing—original draft (lead); writing—review and editing (lead).

## ACKNOWLEDGMENTS

This work was supported by grants from National Key R&D Program of China (2022YFC2504100), and National Natural Science Foundation of China (82171109 and 82025010).

## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest.

## DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

## ETHICS STATEMENT

Not applicable.

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**How to cite this article:** Zhu Z, Zhao C, Wang M. IL-4/IL-13 pathway in nasal type 2 inflammation: the central role and targeted therapy. *Eye & ENT Res.* 2024;1(1):39-48. <https://doi.org/10.1002/eer3.5>