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Research Article

Targeting interleukin-4 and interleukin-13 in the treatment of severe eosinophilic asthma

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Abstract

Asthma is a chronic inflammatory airway disease affecting about 300 million people and responsible for 500,000 deaths annually globally. Eosinophilic asthma is one of the most common phenotypes of asthma. It constitutes about 50% to 60% of all cases of asthma, and it is the most common phenotype in children presenting with severe acute asthma. The mechanism of eosinophilic asthma is chronic airway inflammation which leads to airway hyperresponsiveness, and remodeling due to the immunopathological effects of inflammatory cytokines. The duet cytokines interleukin-4 (IL-4) and IL-13 play the most central role in the pathophysiology of eosinophilic asthma. The two sister cytokines are slightly similar with a 25% homology, they share a common signaling IL-4Rα chain, and have identical biological effects. Their principal biological effect is the development of Th2 cells from naïve T helper type 0 (Th0) lymphocytes. Th2 cells produce several cytokines responsible for inducing airway eosinophilic inflammation. They induce the ε isotype switch and the switching of the B cell immunoglobulin (Ig) production from IgM to IgE. Furthermore, they stimulate eosinophil proliferation, and migration to the allergic airways and promote eosinophil survival by suppressing eosinophil apoptosis. Activated eosinophils secrete several cytotoxic cationic proteins which damage the airway epithelium, and amplify the inflammatory cascade and airway remodeling. Most patients with eosinophilic asthma can achieve control on a long-acting β2-agonist, inhaled corticosteroid, and a leukotriene receptor antagonist. However, about 3.6-10% do not achieve asthma control. These patients usually benefit from treatment with a biologic. Dupilumab is the only biologic targeting IL-4 and IL-13 approved for the treatment of moderate-to-severe eosinophilic asthma. Clinical trials have shown that treatment with dupilumab results in good asthma control, and significantly reduces moderate-to-severe exacerbation rates ($p < 0.001$). Additionally, treatment with dupilumab has been shown to significantly improve lung function ($p < 0.001$), and health-related quality of life, and allows patients to taper or discontinue corticosteroid treatment.

Introduction

Asthma is a chronic inflammatory airway disease affecting about 300 million people and is accountable for 500,000 deaths annually globally [1]. It contributes to a significant healthcare burden and imparts a disproportionate pharmaco-economical cost. The prevalence of asthma has reached a plateau in most developed countries, but it is continuing to rise in low- and middle-income countries [2-4].

Asthma is a heterogenous chronic inflammatory airway disease comprising four phenotypes, classified based on sputum cytology, and biomarkers of airway inflammation [5]. The four phenotypes of asthma include eosinophilic, neutrophilic, paucigranulocytic, and mixed cellularity [5-7]. Eosinophilic asthma constitutes about 50% to 60% of all cases of asthma [8-10] and it is the most common phenotype in children presenting with severe acute asthma [11]. Above all, approximately 40-60% of patients with severe, uncontrolled asthma have an eosinophilic phenotype [12-15].

Eosinophilic asthma is associated with atopy, eczema, allergic rhinitis, Chronic Rhinosinusitis with Nasal Polyps (CRSwNP), Aspirin-Exacerbated Respiratory Disease (AERD) and Eosinophilic Esophagitis (EoE) [16-19]. These diseases significantly increase the severity and burden of eosinophilic

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asthma. Table 1 shows the diseases associated with eosinophilic asthma. Additional features of eosinophilic asthma include elevated blood and sputum eosinophil count and raised Immunoglobulin E (IgE). Unlike neutrophilic asthma, eosinophilic asthma has specific diagnostic biomarkers. They include elevated levels of Fractional exhaled Nitric Oxide (FeNO), raised serum Dipeptidyl Peptidase-4 (DPP-4), periostin, and osteopontin [20-23]. Evaluation of biomarkers of airway inflammation is very useful in stratifying patients for precision, personalized biological therapy because patients with neutrophilic asthma do not respond to eosinophilic targeted biologics.

The pathophysiological mechanism underlying eosinophilic asthma is chronic airway inflammation due to the hypersecretion of cytokines by $CD4^+$ T helper 2 (Th2) cells and innate lymphoid group 2 cells (ILC2). Hematopoietic cells, such as eosinophils, and basophils, and non-hematopoietic cells, including mast cells, epithelial cells, fibroblasts, myofibroblasts, and airway smooth muscle (ASM) cells also secrete Th2 cytokines. The Th2 cytokines consists of interleukin-5 (IL-5), IL-4 and IL-13. Injured or damaged airway epithelium due to viral, bacterial, and fungal infections, aeroallergen, particulate matter, air pollutants, and trauma can generate another set of cytokines known as epithelial cytokines or "alarmins". Alarmin cytokines include IL-25, IL-33 and Thymic Stromal Lymphopoietin (TSLP).

Conversely, Th1 cells secrete interleukin-12, interferon-α (IFN-α), IFN-γ and transforming growth factor-β, which play an inhibitory role in Th2 cytokine production and eosinophilic inflammation. Interferon-γ has an inhibitory effect on IgE production, eosinophilic functions, and eosinophilic inflammation. In children with moderate asthma, it has been shown that the concentration of IFN-γ in supernatants of cultures of stimulated Peripheral Blood Mononuclear Cells (PBMCs) was significantly lower and the ratio of IFN-γ/IL-4 was also significantly lower [24]. This indicates that during eosinophilic inflammation in asthmatic patients, there is excessive production of Th2 cytokines, such as Il-5, IL-4 and Il-13 and suppression of the secretion of Th1 cytokines, including IFN-β.

During an asthmatic response, there is the activation of Th2, ILC2, epithelial cells, hemopoietic, and non-hemopoietic cells. This results in the secretions of both Th2 and epithelial cytokines, chemokines, adhesion molecules, and growth factors. These inflammatory mediators result in eosinophilic inflammation, Airway Hyperresponsiveness (AHR) and remodeling.

Table 1: Diseases associated with eosinophilic asthma.

Food allergy
Allergic rhinitis
Atopic dermatitis
Allergic rhinitis
Eosinophilic asthma
Chronic rhinosinusitis with nasal polyps (CRSwNP)
Aspirin exacerbated respiratory disease
Eosinophilic esophagitis

Airway remodeling is responsible for airway narrowing, severe airway obstruction and difficult-to-treat eosinophilic asthma. The airway structural changes which occur during the remodeling crusade include laying of the extracellular matrix proteins secreted by fibroblasts and myofibroblasts, subepithelial fibrosis and thickening, goblet cell hyperplasia and mucus hypersecretion, airway smooth muscle hyperplasia and hypertrophy, and neovascularization. Airway remodeling ultimately leads to airway wall thickening, severe airway obstruction, and severe asthma. Furthermore, airway remodeling results in difficulty to control asthma with the Standard of Care (SoC), which includes Long-Acting β2-Agonists (LABA) and low-dose Inhaled Corticosteroids (ICS).

Interleukin-4

The duet sister cytokines IL-4 and IL-13 play a key role in the pathogenesis of eosinophilic asthma and other allergic diseases, such as atopic dermatitis, allergic rhinitis, chronic rhinosinusitis with nasal polyps, and aspirin-exacerbated respiratory disease.

Interleukin-4 is a pleiotropic type 1 cytokine that controls the growth and differentiation of immune, hematopoietic, and non-hematopoietic cells. It was simultaneously discovered by two separate groups led by Maureen Howard, William E. Paul; and Ellen Vitetta, in 1982 [25]. It was initially identified as a soluble factor responsible for B-cell proliferation, and as a class-switching cytokine [26].

Interleukin-4 is a compact, globular cytokine, stabilized by three disulfide bonds. One-half of the molecule is composed of a four alpha-helix bundle and is closely related to IL-13 with a 25% homology. Interleukin-4 and IL-13 are encoded by adjacent genes located on chromosome 5q31-33 and are closely linked to one another [27]. They share a number of regulatory elements, such as GATA-3 [28] and transmit signals through a shared functional receptor complex (IL-4Rα/IL-13Rα1) [29]. IL-4 and IL-13 have almost the same biological effects, although each of these cytokines has its own independent immunopathological functions.

Interleukin-4 plays a central role in the pathogenesis of severe eosinophilic asthma [30-32]. It is secreted mainly by Th2 lymphocytes [33,34], and ILC2 cells [35,36]. IL-4 is also produced by mast cells, eosinophils and basophils [37,38].

Interleukin 4 controls both the growth and differentiation of immune, hemopoietic and non-hemopoietic cells. It is a key factor for the development of Th2 cells from naïve T helper type 0 (Th0) lymphocytes. Th2 cells produce and secrete several cytokines, and chemokines responsible for inducing allergic reactions, including IL-4 in a positive feedback loop. Interleukin-4 also controls ILC2 cells and Natural Killer (NK) T cells proliferation, which contribute to airway inflammation, and eosinophilic asthma by secretion of Th2 cytokines, and chemokines [39,40].

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Interleukin-4 has several other biological and immunological effects. Most importantly, it induces the ε isotype switch and switching of B cell immunoglobulin production from IgM to IgE [41,42]. Additionally, IL-4 enhances IgE-mediated responses by upregulating IgE receptors on various immune cells, such as the high-affinity IgE receptors (FcεRI) on mast cells and basophils, and the low-affinity IgE receptors (FcεRII; CD23) on lymphocytes and mononuclear cells [30,43]. IgE plays an important role in activating mast cells, eosinophils, and basophils, which upon activation degranulate and release numerous cationic proteins, cytokines, chemokines, growth factors and enzymes. These inflammatory mediators are responsible for airway epithelial injury, eosinophilic inflammation, AHR and airway remodeling.

Interleukin-4 stimulates the migration of eosinophils into allergic airways through increases in the expression of eotaxin 1, 2 and 3 [44,45]. It also prolongs eosinophil survival by preventing eosinophil apoptosis [46]. Activated eosinophils degranulate and release several cytotoxic cationic proteins, such as Major Basic Protein (MBP), Eosinophil Cationic Protein (ECP), Eosinophil-Derived Neurotoxin (EDN) and Eosinophil-Derived Peroxide (EDPX) [47]. In addition, eosinophils release mediators, such as leukotrienes, prostaglandins, cytokines, chemokines, enzymes, and reactive oxygen species. These inflammatory mediators cause epithelial injury, bronchial smooth muscle contraction, microvascular leakage and airway edema, goblet cell hyperplasia, and mucus secretion [48-50]. Table 2 shows the inflammatory mediators secreted by activated eosinophils.

The cationic proteins (MBP, ECP, EDN, and EDPX) are very cytotoxic to the airway epithelium and myelinated neurons and can cause epithelial and neuronal injury, and damage. EDPX forms reactive oxygen species and reactive nitrogen metabolites that promote oxidative stress, causing cell death by apoptosis and necrosis of epithelial cells. Furthermore, eosinophilic cation proteins are associated with airway smooth muscle hypertrophy, AHR, and airway remodeling [48-50].

Interleukin-4 induces mucin-encoding gene (MUC5AC) expression which results in goblet cells hyperplasia, and mucus hypersecretion, which can obstruct the airways and cause severe airflow limitation [51]. Accumulation of sticky mucus causes diffuse airway obstruction and is an important feature of severe, near-fatal, and fatal asthma [52].

Interleukin-4 has been demonstrated to have 15-lipoxygenase activity, and to promote the production of Leukotrienes (LT), such as LTB4, LTC4, and LTD4 [53]. Leukotrienes are potent bronchoconstrictor, secretagogues, and vasodilators and promote vascular leakage, resulting in airway mucosal edema. This may lead to severe airway obstruction.

IL-4 also plays an important role in the proliferation of fibroblasts, and myofibroblasts, which deposit extracellular matrix (ECM proteins). This leads to subepithelial fibrosis and thickening of the basement membrane, airway remodeling, and partially irreversible airflow limitation [54].

Another biological effect of IL-4 is the induction of adhesion molecule production, such as Vascular Cell Adhesion Molecule-1 (VCAM-1), Intercellular Adhesion Molecule-1 (ICAM-1) and E-selection by vascular endothelial cells. VCAM-1 and ICAM-1 are responsible for the lining of inflammatory cells along the blood vessel wall. VACM-1 or ICAM-1 and IL-4 facilitate diapedesis and migration of eosinophils, basophils, T lymphocytes, and mast cells from blood vessels to the inflamed allergic airways. Activation of these cells amplifies eosinophilic airway inflammation by secreting more cytokines, chemokines, adhesion molecules, and enzymes which orchestrate eosinophilic inflammation, and airway remodeling. Table 2 shows the cationic proteins and pro-inflammatory mediators synthesized and secreted by activated eosinophils.

Interleukin-4 signaling

The interleukin-4 receptor complex (IL-4R) is a heterodimer composed of a common α-subunit (IL-4Rα), and the γc chain to form the IL-4R type I. The γc subunit also functions as a subunit for other cytokines, such as IL-2, IL-7, IL-9, IL-15, and IL-21 receptor complexes. Type I receptor is expressed predominantly on several hematopoietic cells and binds exclusively to IL-4 [55,56]. IL-4Rα also binds to the IL-13 receptor (IL-13Rα1), to form a high-affinity type II heterodimeric complex (IL-4Rα/IL-13Rα1), which binds to both IL-4, and IL-13. Interleukin-4 signals through both types I and II receptors, whereas IL-13 signals only through type II [55,56]. Type II IL-4/IL-13 receptor binds to hematopoietic cells, and non-hematopoietic cells, such as epithelial cells, fibroblasts, and airway smooth muscle cells to mediate the immunopathological effects of both IL-4 and IL-13 [57].

The binding of IL-4 to its receptors stimulates the transphosphorylation and activation of receptor subunits of the Janus Family Protein Kinases (JAKs), such as JAK1, JAK2, JAK3, and Tyrosine Kinase (Tyk2) [58-61]. Type I receptors

Table 2: Cationic protein and pro-inflammatory mediators are synthesized and secreted by activated eosinophils.

Eosinophil Cationic Protein (ECP)
Major Basic Protein (MBP)
Eosinophil-Derived Neurotoxin (EDN)
Eosinophil-Derived Peroxide (EDPX)
Reactive oxygen species: superoxide, peroxide and hypobromite
Prostaglandins: PGD2
Cysteinyl leukotrienes: LTC4, LTD4, LTE4
Thromboxane B2: TXB2
Platelet-Activating Factor (PAF)
Cytokines: IL-2, IL-3, IL-4, IL-5, IL-9, IL-13, IL-23, IL-25, IL-33, and TNF-α, GM-CSF
Chemokines: eotaxin-1, -2, and -3, RANTES, P-selectin, MIP-1, MCP-3, MCP-4
Enzymes: histaminases, arylsulfatase, MMP-9, TIMP-1
Growth factors: TGF-β, VEGF, PDGF

Abbreviations: LT: Leukotriene; IL: Interleukin; MMP: Matrix Metalloproteinases; TIMP: Tissue Inhibitors of Metalloproteinases; MIP: Macrophage Inflammatory Protein; MCP: Monocyte Chemoattractant Protein; GM-CSF: Granulocyte-Macrophage Colony-Stimulating Factor; TGF-β: Transforming Growth Factor-β; VEGF: Vascular Endothelial Growth Factor; PDGF: Platelet-Derived Growth Factor.

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activate Jak1 and Jak3, type II receptors activate Jak1, Jak2, and Tyk2 [62,63].

Activation of the JAK family initiates phosphorylation of specific tyrosine residues of the cytoplasmic domain of the IL-4Rα [64-67]. Phosphorylation of the three tyrosine residues IL-4Rα Y575, IL-4α 603 and IL-4Rα Y633 leads to the recruitment of the transcription factor Signal Transducer and Activator of Transcription 6 (STAT6), through the domains of STAT6 [66]. STAT6 molecules in turn are phosphorylated, dimerized, and translocate to the nucleus where they regulate gene transcription leading to the production of Th2 cytokines, and chemokines involved in the pathogenesis of eosinophilic asthma [68,69]. Gene transcription leads to the secretion of Th2 cytokines, such as IL-3, IL-4, IL-5, and GM-CSF and chemokines, including CCL11 (eotaxin 1), CCL24 (eotaxin 2), CCL26 (eotaxin 3), CCL13 (MCP4) and CCL5 (RANTES) [70,71].

Both types I and II receptors initiate activation of the STA6 pathway [72], but only type I IL-4 receptors activate the Insulin Receptor Substrate (IRS-2) pathway [73,74]. However, activation of type II receptors and STAT6 is essential for most of the features of eosinophilic asthma [75].

Interleukin-13

Interleukin-13 (IL-13) plays a pivotal role in the pathogenesis of severe eosinophilic asthma [76,77]. It is produced by activated Th2 lymphocytes [78,79], ILC2 cells [80,81], B cells [82], mast cells [83-85], macrophages [86], eosinophils [87,88] and basophils [89,90].

Interleukin-13 was initially discovered in 1993 and was identified by molecular cloning in activated human T-lymphocytes [91]. It has a molecular weight of 13 kDa and is composed of four alpha helical bundles, A, B, C and D. It shares 25% sequence homologies with interleukin-4; however, it is capable of independent signaling, and distinctive immunobiological functions [92,93]. Interleukin-13 plays the most important role in the pathogenesis of severe, uncontrolled eosinophilic asthma [94,95].

Like its sister IL-4, IL-13 also plays an important role in switching B-cell immunoglobulin production from IgM to IgE and IG1 [96,97]. It promotes eosinophil recruitment and activation into inflamed airways [98] and fosters eosinophil survival by preventing apoptosis [99,100]. Additionally, IL-13 induces goblet cell hyperplasia and mucus hypersecretion [101-104]. Goblet cell hyperplasia and mucus overproduction are features of severe asthma. Excessive airway mucus plugging due to thick tenacious mucus is associated with fatal asthma [105].

Interleukin-13 stimulates the proliferation of fibroblasts [106,107] and myofibroblasts [108,109]. It is responsible for the deposition of ECM proteins produced by fibroblasts, and myofibroblasts, leading to subepithelial fibrosis, airway wall thickening, AHR and remodeling [108]. Additionally, IL-13 induces ASM cell proliferation [110,111] and enhances differentiation and contractility of airway smooth muscle cells *via* up-regulation of the RhoA protein [112]. Interleuki-13 has been shown to enhance the proliferation of ASM cells, and in enhancing the cholinergic-induced contraction of ASM cells [113], thus intensifying severe bronchoconstriction in asthma.

Interleukin-13 increases the activity of vascular cell adhesion molecules, such as β-integrin, VACM-1 and ICAM-1 [114,115], which promote eosinophilic migration and recruitment in allergic airways, thus promoting eosinophilic inflammation. IL-13 is a very potent inducer of VACM-1 on endothelial cells and plays a major role in eosinophil migration from the blood vessels, and recruitment into allergic airways [116]. The recruited activated eosinophils liberate more cytotoxic cationic proteins, cytokines, chemokines, and reactive oxygen species, which intensify airway inflammation, AHR, and remodeling.

Additionally, IL-13 induces the expression of Vascular Endothelial Cell Growth Factors (VEGF-A, B, C, D, E, F. VEGFA (VEGF) is one of the most powerful and potent endothelial cell mitogens. It promotes angiogenesis in asthmatic airways, expanding the airway vascular network, which contributes to airway remodeling and severe asthma [117-119].

Interleukin-13 induces the expression of pro-fibrotic matricellular proteins periostin and osteopontin [120,121]. Periostin and osteopontin play an important role in fibroblast activation and increase collagen gel elasticity. They play a central role in promoting fibroblast and myofibroblast proliferation, subepithelial fibrosis, and mucus hypersecretion which lead to progressive structural changes in the airways [120,121]. Periostin-induced airway remodeling leads to a progressive decline in lung function (forced expired volume in one second, FEV1) and fixed airflow limitation [122,123].

Furthermore, periostin is associated with corticosteroid resistance. It induces a reduction in the affinity of the glucocorticoid receptor in inflammatory cells, such as T cells, and monocytes, resulting in local resistance to the anti-inflammatory effects of corticosteroids [124,125]. Interleukin-13 induces activation of epithelial nitric oxide synthase through its effect on STAT-6 [126], which results in the production of exhaled nitric oxide from airway epithelial cells. Fractional exhaled nitric oxide mirrors IL-13 biological activity and is a pharmacodynamic biomarker of eosinophilic asthma [127,128]. Table 3 shows the immunopathological mechanisms of IL-4/13 in the pathogenesis of severe eosinophilic asthma.

Interleukin-13 signaling

Interleukin-13 signaling is via IL-13 receptors (IL-13Rs) which are heterodimer complexes consisting of an IL-13Rα1 or IL-13Rα2 chain, bound to an IL-4Rα chain. However, IL-13 mediates most of its effects by binding to IL-13Rα1 and IL-4Rα (type II receptor) [129,130]. The IL-4Rα chain is similar to both IL-4 and IL-13, and shares similarities in signal transduction, and in the regulation of antibody production, and allergic inflammation. However, IL-13 is capable of independent signaling and has some different immunopathologic functions from those of IL-4. Nevertheless, the signaling pathways are common to both receptors and are largely JAK-STAT6-

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Table 3: Immunopathological mechanisms of IL-4/13 in the pathogenesis of severe eosinophilic asthma.
Switch of B cell antibody production from IgM to IgE
Stimulating the production of immunoglobulin E (IgE)
Eosinophilopoiesis
Recruitment and activation of eosinophils, basophils and Th2 lymphocytes
Preventing eosinophil apoptosis
Epithelial-mesenchymal transition
Secretion of IL-25, IL-33, and thymic stromal lymphopoietin (TSLP)
Goblet cell differentiation, hyperplasia, mucus production, and secretion
Stimulation of production of eotaxins, and vascular adhesion molecules
Stimulation of inducible nitric oxide synthase, and production of nitric oxide
Secretion of periostin and osteopontin
The proliferation of bronchial fibroblasts, and myofibroblasts
Subepithelial fibrosis, and thickening of basement membrane
Differentiation and proliferation of airway smooth muscle cells
Airway hyperresponsiveness
Airway remodeling
Corticosteroid-resistance

dependent. The binding of IL-13 to type II receptors leads to the activation of JAK1, JAK2 and tyrosine kinase 2 (TYK2). Activation of JAKS leads to the recruitment of STAT6 to the receptors, with subsequent phosphorylation and dimerization of STAT6. Activated STAT6 dimers translocate to the nucleus, where they bind to specific DNA elements, and result in the transcription of downstream genes [58,59]. This results in the production of several cytokines, and chemokines by immune cells, such as Th2 lymphocytes, ILC2 cells, eosinophils, mast cells, and macrophages. IL-13 can also bind to the high-affinity IL-13Rα2. Signaling through this receptor has been reported to induce TGF-β production in mice and humans, and promotion of fibrosis [60].

Treatment of severe eosinophilic asthma

Most patients with eosinophilic asthma respond to treatment with standard therapies, such as Long-Acting β-Agonists (LABA), Low-Dose Inhaled Corticosteroids (ICS) and Leukotriene Receptor Antagonists (LTRA). For patients who still experience asthma exacerbations, the addition of a Long-Acting Muscarinic Antagonist (LAMA) usually can control asthma. Patients with severe, uncontrolled eosinophilic asthma can benefit from a single inhaler dual therapy, or a Single Inhaler Triple Therapy (SITT), comprising a LABA, an ICS, and a LAMA in a single inhaler. SITT is very effective in treating difficult-to-control asthma, and it improves compliance [61,131,132]. Single inhaler triple therapy significantly reduces moderate-to-severe exacerbations and improves lung function (FEV1) compared with single inhaler dual therapy. In the TRIMARAN clinical trial, Virchow, et al. [61] have shown that SITT significantly reduced moderate-to-severe exacerbation ($p < 0.033$), and significantly improved FEV1 ($p < 0.008$) compared with single inhaler dual therapy [61]. Table 4 shows drug combinations in the single-inhaler dual therapy and single-inhaler triple therapy.

However, about 15% - 20% of patients with asthma remain uncontrolled, with frequent exacerbations, increased use of ICS or OCS, recurrent emergency room admissions, and impaired quality of life [133]. Approximately, 3.6% - 10% of asthmatics have severe refractory corticosteroid-resistant disease, which is uncontrolled despite treatment with high dose ICS, LABA, and/or LTRA [134,135]. About 50% of these patients have Th2-mediated severe eosinophilic asthma.

Treatment of patients with severe eosinophilic asthma may necessitate the use of biologics. There are several monoclonal antibodies (mAb) targeting the inflammatory cytokines implicated in the pathophysiology of eosinophilic asthma. There is only one biologic targeting IL-4 and IL-13 signaling pathways that have been approved for the treatment of moderate-to-severe eosinophilic asthma in adults and children 12 years and older. Dupilumab (Dupixent®) is a fully humanized IgG4 monoclonal antibody to the IL-4Rα, which mediates signaling to both IL-4 and IL-13. It was approved for the treatment of moderate-to-severe asthma on October 19, 2018. It is administered subcutaneously. In adults and children 12 years and older, it is administered as 400 mg (two 200 mg injections) as the initial loading dose. Thereafter, the subsequent dose is 200 mg every two weeks.

In most clinical trials, dupilumab has been shown to improve asthma control, and significantly reduce exacerbations ($p < 0.001$) compared with a placebo. Additionally, it has been demonstrated to significantly improve lung function ($P < 0.001$), and health-related quality of life (HLQoL) and allow patients to taper or discontinue corticosteroids [136-139] compared with placebo.

Dupixent is also approved for the treatment of eczema [140,141], chronic rhinosinusitis with nasal polyps [142,143] and eosinophilic esophagitis [144]. Comorbid diseases, particularly CRSwNP and EoE make asthma control very difficult unless

Table 4: Single-inhaler dual and triple therapy combinations for the treatment of severe eosinophilic asthma.
Single-inhaler dual therapy - LABA/LAMA
Formoterol – Glycopyrrolate
Formoterol – Aclidinium
Vilaterol – Umclidinium
Olodaterol – Tiotropium
Single-inhaler dual therapy - LABA/ICS
Albeterol - Budesonide
Salmeterol – Fluticasone propionate
Formoterol – Beclomethasone dipropionate
Formeterol – Budesonide
Formeterol – Mometasone
Vilanterol – Fluticasone
Indacerol – Mometasone
Single-inhaler triple therapy - LABA/LAMA/ICS
Beclomethasone dipropionate – Formeterol – Glycopyrronium
Budesonide – formoterol – Gylcopyrronium
Fluticasone fuorate – Vilanterol – Umeclidinium

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the associated diseases are treated adequately. Dupilumab is beneficial and effective in treating severe eosinophilic asthma in patients with the above comorbidities [145].

Recently, dupilumab has been shown to have a long-term effect and safety for 96 weeks in patients with asthma with or without chronic rhinosinusitis and nasal polyps [146] and for 148 weeks in patients with moderate-to-severe asthma [147]. Notably, it reduces oral corticosteroid use in patients with corticosteroid-dependent asthma [146,148], thus reducing the serious side effects due to prolonged corticosteroid treatment.

Conclusion

The duet sister cytokines IL-4, and IL-13 play a central role in the pathogenesis of eosinophilic asthma. IL-4 and Il-13 are related and they share the same signaling pathway via the IL-4R chain and have similar biological functions. Most patients with eosinophilic asthma respond to a LABA, low-dose ICS, and LTRA. However, approximately 3.6-10% are refractory to the treatment, including oral corticosteroids (OCS). These patients benefit from treatment with a biologic. Dupilumab is the only approved biologic that inhibits the biological and immunological effects of both IL-4 and IL-13. Treatment with dupilumab results in good asthma control, reduction in exacerbation rates, improvement in lung function, and HLQoL. Noteworthy, Dupilumab is also very useful in ameliorating the comorbid allergic diseases associated with eosinophilic asthma.

Conflict of interest

The author declares that the publication was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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