



Interleukin-4/interleukin-13 versus interleukin-5: a comparison of molecular targets in biologic therapy for the treatment of severe asthma

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Purpose of review

Asthma is a chronic, inflammatory disorder of the airways caused by a complex interplay of various biologic mechanisms. Several monoclonal antibody therapies targeting interleukin (IL)-4/IL-13 and IL-5 cytokine pathways have been developed for the treatment of severe eosinophilic asthma. As individuals can display biomarkers and clinical features characteristic of several asthma phenotypes, selection of an optimal biologic can be difficult.

Recent findings

Dupilumab, a monoclonal antibody that binds to the α subunit of the IL-4 receptor (IL-4R α) and has been approved for the treatment of adults with severe atopic dermatitis, has been shown in recent phase 3 trials to also have significant clinical benefits in the asthmatic population irrespective of baseline eosinophil counts.

Summary

As monoclonal antibodies targeting either IL-4 or IL-13 cytokines individually have failed to demonstrate significant clinical benefits, biologics that target cytokine receptors may be more efficacious compared to those that target cytokines. Furthermore, inhibition of the IL-4/IL-13 signaling cascades may disrupt a broader Th2 inflammatory response compared to a more selective impairment of eosinophil proliferation and activity via blockage of the IL-5 pathway. Future research with independently funded, head-to-head trials of approved biologics is needed to elucidate a favorable therapeutic option.

Keywords

biologics, interleukin-13, interleukin-4, interleukin-5, severe asthma

INTRODUCTION

Asthma is a chronic, inflammatory disorder of the airways caused by a complex interplay of various biologic mechanisms [1]. Our understanding of asthma has evolved over the past several decades with type-2 inflammation thought to be central to the pathogenesis of asthma [2]. Biologic agents targeting cytokines produced by Th2 lymphocytes have allowed for the inhibition of specific inflammatory pathways, and several anti-interleukin (IL)-5 and IL-5 receptor monoclonal antibodies (mepolizumab, reslizumab and benralizumab) have been utilized successfully in the treatment of severe eosinophilic asthma [3]. Dupilumab, a monoclonal antibody (mAb) that binds to the α subunit of the IL-4 receptor (IL-4R α) and has been approved for the treatment of adults with severe atopic dermatitis, has recently been shown in phase 3 trials to also have favorable results in patients with uncontrolled, moderate-to-severe asthma [4^{••}–6^{••}]. As new biologics emerge in the treatment of asthma, the question of which

therapy is most suitable has become more prevalent and an understanding of the molecular pathways involved increasingly important. Here, we review the IL-4/IL-13 and IL-5 signaling cascades targeted by these biologics and assess their potential impact on precise patient populations.

INTERLEUKIN-4/INTERLEUKIN-13 CYTOKINES: HISTORY, PATHWAY AND ROLE IN ASTHMA PATHOGENESIS

Discovered in the early 1980s, IL-4 and IL-13 are two similar cytokines that have been implicated in a

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KEY POINTS

- Increasing numbers of biologic agents targeting IL-4/IL-13 and IL-5 pathways have been developed for the treatment of severe eosinophilic asthma, and selection of an optimal biologic can be difficult.
- Asthma is a complex, heterogeneous disease and individuals can display biomarkers and clinical features characteristic of several asthma phenotypes, thus ruling them eligible for several biologics.
- Monoclonal antibodies that target cytokine receptors and prevent signal transduction may be more clinically efficacious compared to those that target cytokines.
- Inhibition of the IL-4/IL-13 signaling cascade may disrupt a broader Th2 inflammatory response compared to blockage of the IL-5 pathway.
- Further research with independently funded, head-to-head trials of approved biologics is needed to elucidate a favorable therapeutic option.

variety of biologic processes, particularly in the pathogenesis of asthma and atopic disease [7]. Found adjacent to one another on human chromosome 5 and often coordinately expressed by Th2 lymphocytes, both cytokines play crucial roles in type-2 inflammation [8]. Binding of IL-4 or IL-13 to the IL-4 receptor activates kinases that phosphorylate signal transducer and activator of transcription factor 6 (STAT6), which dimerizes and translocates to the nucleus (Fig. 1). STAT6 then induces the expression of GATA3, a transcription factor that promotes the expression of a type-2 cytokine milieu that mediates a multitude of proinflammatory functions in asthma. Although it was originally thought that IL-4 and IL-13 served redundant functions because of a shared receptor and common regulatory pathways, recent studies indicate distinctive and divergent roles of the two cytokines in the pathogenesis of asthma.

Two different IL-4 receptor complexes, type I and type II, are now known to initiate IL-4 and IL-13 signaling [9]. The type I receptor, found primarily on hematopoietic cells, is composed of IL-4R α and γ_c subunits and exclusively binds IL-4, upon which Janus kinase 1 and 3 (JAK1 and JAK3) are activated. The type II receptor, found primarily on nonhematopoietic cells, is composed of IL-4R α and IL-13R α 1 subunits and thus binds to both IL-4 and IL-13, which subsequently activates tyrosine kinase 2 (TYK2) and JAK1. Studies have attributed the differing roles of IL-4 and IL-13 to the selective expression of type I and II receptors among various cell types as well as to differences in cytokine affinity for the

receptors. Because T cells often exhibit only type I receptors, their activity is stimulated primarily by IL-4. Thus, IL-4 is more prominently implicated in Th2 cell differentiation. Stimulation of type I receptors also activates the insulin receptor substrate-2 pathway, which provides protection against apoptosis [10]. Expression of type II receptors is limited to the lungs, including airway epithelial, endothelial and smooth muscle cells, and fibroblasts. Although the type II receptor is stimulated by both IL-4 and IL-13, IL-13 is thought to have a greater affinity and plays a larger role in the physiological responses of type-2 inflammation in the airway, such as mucous production via stimulation of goblet cells, airway smooth muscle contraction, subepithelial fibrosis, airway hyper-reactivity and eosinophil activity in the lungs [11,12].

Many studies have shown the fundamental role of IL-4 and IL-13 in eosinophil recruitment to the airways. Binding of either cytokine to the type II IL-4 receptors on airway endothelial cells induces the expression of VCAM-1, which binds to eosinophil and basophil integrin (VLA-4) and mediates the adhesion and accumulation of eosinophils and basophils in lung tissue [13,14]. In response to IL-4 or IL-13 binding to IL-4R α , airway smooth muscle cells express the chemokine eotaxin, which serves as a direct chemoattractant for eosinophils [15,16]. Furthermore, periostin is an inducible product secreted from bronchial epithelial cells and fibroblasts due to IL-4 or IL-13 stimulation. Periostin, an extracellular matrix protein that upregulates TGF- β and type 1 collagen resulting in subepithelial fibrosis, has also been shown to mediate allergen-induced eosinophil infiltration into lung tissue and promote eosinophilic airway inflammation [17,18].

ANTI-INTERLEUKIN-4/INTERLEUKIN-13 BIOLOGICS FOR MODERATE-TO-SEVERE ASTHMA

Because of the important roles of IL-4 and IL-13 in asthma, therapies targeting these cytokines were developed with mixed results. Phase 1 trials of pascolizumab, an early anti-IL-4 mAb, demonstrated the inhibition of T-cell proliferation and IgE production [19]. However, phase 2 trials did not reduce circulating IgE levels or demonstrate clinical benefit in steroid-naïve asthmatic patients [20]. Lebrikizumab, amAb targeting IL-13, was shown in phase 2 trials to improve FEV1 in asthmatic patients compared to placebo, with patients with higher serum periostin levels demonstrating greater improvements [21]. Two subsequent phase 3 studies, Lavolta I and Lavolta II, did not consistently show clinically

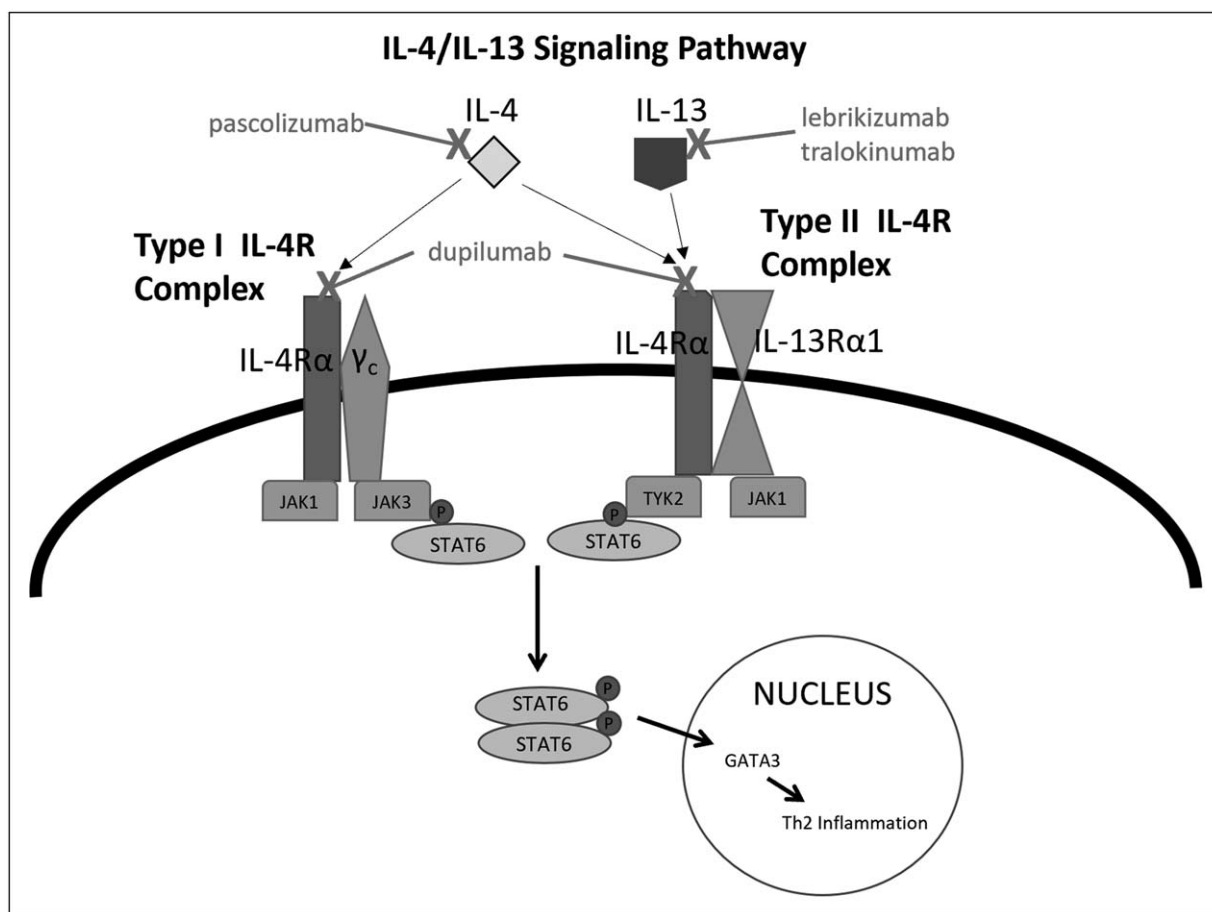


FIGURE 1. IL-4 can bind to either the type I (IL-4R α and γ_c) or type II (IL-4R α and IL-13R α 1) IL-4 receptor complexes, whereas IL-13 binds only to the type II IL-4 receptor complex. Binding of IL-4 to the type I receptor activates JAK1 and JAK3, whereas binding of IL-4 or IL-13 to the type II receptor activates TYK2 and JAK1. The kinases then phosphorylate STAT6, which dimerizes and translocates to the nucleus and induces the expression of GATA 3, a transcription factor that promotes the expression of Th2 inflammatory mediators. Pascolizumab is monoclonal antibody against the cytokine IL-4, and lebrikizumab and tralokinumab are monoclonal antibodies against IL-13. Dupilumab binds to IL-4R α and inhibits IL-4 and IL-13 signaling through the type I and type II IL-4R complexes.

significant improvements in lung function or asthma exacerbations regardless of serum periostin and blood eosinophil concentrations [22]. Tralokinumab, another anti-IL-13 mAb that showed promising results in phase 2 trials, also failed to show benefit in three subsequent phase 3 trials [23,24].

Dupilumab is a human monoclonal antibody that binds to IL-4R α and inhibits both IL-4 and IL-13 signaling pathways [25]. Approved in March 2017 for the treatment of adults with moderate-to-severe atopic dermatitis, dupilumab has undergone several recent clinical trials demonstrating benefit in patients with moderate-to-severe asthma, regardless of levels of type-2 inflammatory biomarkers or minimum baseline eosinophil levels [4th–6th,25]. A proof-of-concept phase 2a study examining the use of dupilumab in patients with severe asthma and elevated blood and sputum eosinophil levels

showed improvements in asthma exacerbation rates, FeNO and FEV1 [26]. No reductions in blood or sputum eosinophils were observed, although the sample size of patients who contributed sputum samples was very small and likely statistically insignificant. A subsequent larger, pivotal phase 2b study again showed improved FEV1 and asthma exacerbation rates in patients treated with dupilumab compared to placebo, irrespective of blood eosinophil counts, though patients with eosinophil counts of at least 300 cells/ μ l had greater benefit [27].

In the more recent phase 3 VENTURE trial, patients age 12 or older with oral glucocorticoid-treated asthma receiving dupilumab add-on therapy showed steroid-sparing benefits with significant reductions in maintenance oral steroid dose, decreased rates of severe exacerbations and increased FEV1 compared to the placebo group

[4^{***}]. Although the treatment arm showed positive results in the overall population versus placebo, patients with higher baseline blood eosinophil counts (≥ 300 cells/ μ l) and FeNO levels had greater benefit. The phase 3 QUEST trial also demonstrated benefit in moderate-to-severe asthmatic adolescents and adults treated with dupilumab compared to placebo, with the treatment group exhibiting reduced rates of severe exacerbations, increased FEV1, as well as improvements in asthma quality of life and control scores (AQLQ and ACQ) [5^{***},6^{***}]. Like the VENTURE trial, patients with more elevated baseline blood eosinophil counts (≥ 150 cells/ μ l) and FeNO levels (≥ 25 ppb) had greater improvements compared to the overall population. Both the VENTURE and QUEST trials noted a transient increase in peripheral eosinophilia in the dupilumab group compared to placebo, which the authors attributed to the blockage of localized eosinophil recruitment despite continued bone marrow synthesis. A decrease in FeNO levels was shown in the dupilumab group in both trials, and in the QUEST trial, the treatment group also showed reductions in total IgE, eotaxin-3, periostin and thymus and activation-regulated chemokine levels, which the authors suggest illustrates a more comprehensive inhibition of type-2 inflammation than selective targeting of eosinophils with anti-IL-5 therapies.

Recent studies have evaluated the use of dupilumab in patients with chronic sinusitis and nasal polyps [28,29^{*}]. Chronic rhinosinusitis with nasal polyps is a disease associated with an increase in asthma prevalence, particularly eosinophilic asthma [30]. Both diseases share histopathological similarities, and Th2 inflammation is thought to play a role in the association of both diseases. The combination can be very difficult to treat, and studies have shown improvements of asthma after medical and/or surgical treatment of chronic rhinosinusitis with nasal polyps. A small, proof-of-concept phase 2 study initially showed that the addition of dupilumab to adults with symptomatic chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids exhibited improvements in endoscopic nasal polyp burden, sinus imaging scores, sinonasal quality of life scores and sense of smell assessments [28]. Patients with comorbid asthma had improvements in lung function and asthma control endpoints. A larger, recently completed study further evaluated the efficacy of dupilumab in improving polyp burden, clinical symptoms and radiographic findings in patients with bilateral nasal polyposis, though results have not yet been released [29^{*}]. As dupilumab has shown benefit in several diseases with the involvement of Th2 inflammation, it may be a candidate for the treatment of a variety of asthma subphenotypes and

help mitigate the broad range of disease heterogeneity in asthma.

INTERLEUKIN-5: HISTORY, PATHWAY AND ROLE IN EOSINOPHIL MATURATION AND FUNCTION

IL-5 is a proinflammatory cytokine produced by Th2 cells and mast cells that plays a crucial role in the differentiation, proliferation, survival and effector functions of eosinophils [31]. The IL-5 receptor is composed of a ligand-specific α chain, IL-5R α , and a β chain, which is shared with the IL-3 and granulocyte-macrophage colony-stimulating factor (GM-CSF) receptors. Their ligands, IL-3 and GM-CSF, are also of importance in the differentiation and survival of eosinophils. During eosinophilopoiesis, CD34⁺ bone marrow progenitor cells acquire IL-5R α early and commit to the eosinophil lineage under the influence of IL-5. Binding of IL-5 to its receptor activates multiple signaling proteins, including protein tyrosine kinases (e.g. Lyn and JAK2), which signal through the Ras-Raf-MEK-ERK and JAK-STAT pathways to inhibit apoptosis and promote eosinophil survival (Fig. 2) [32]. Raf-1 kinase also plays crucial roles in eosinophil function via upregulation of eosinophil adhesion molecules (CD11b), induction of superoxide and leukotriene production and stimulation of degranulation [33]. Once eosinophils infiltrate the airways, they produce IL-5, thus creating a positive feedback mechanism. Furthermore, eosinophil cytotoxic secondary granules containing four cationic proteins are released, resulting in the production of reactive oxygen species, lysis of epithelial cells and antigen penetration. A number of proinflammatory mediators are also synthesized and secreted, further contributing to the myriad of inflammatory cascades involved in airway inflammation. Early studies have shown increased levels of IL-5 and eosinophils in serum and BAL fluid of asthmatic patients compared to healthy individuals, demonstrating a crucial role of IL-5 in the pathogenesis of asthma [34]. Eosinophilic asthma is a unique asthma phenotype that has become increasingly recognized, with biologic therapies targeting IL-5 pathways now commonly used in the treatment of severe eosinophilic asthma refractory to inhaled corticosteroids, bronchodilators and leukotriene antagonists [3].

ANTI-INTERLEUKIN-5 BIOLOGICS FOR MODERATE-TO-SEVERE EOSINOPHILIC ASTHMA

Important clinical trials have supported the use of IL-5 targeted therapies for eosinophilic asthma.

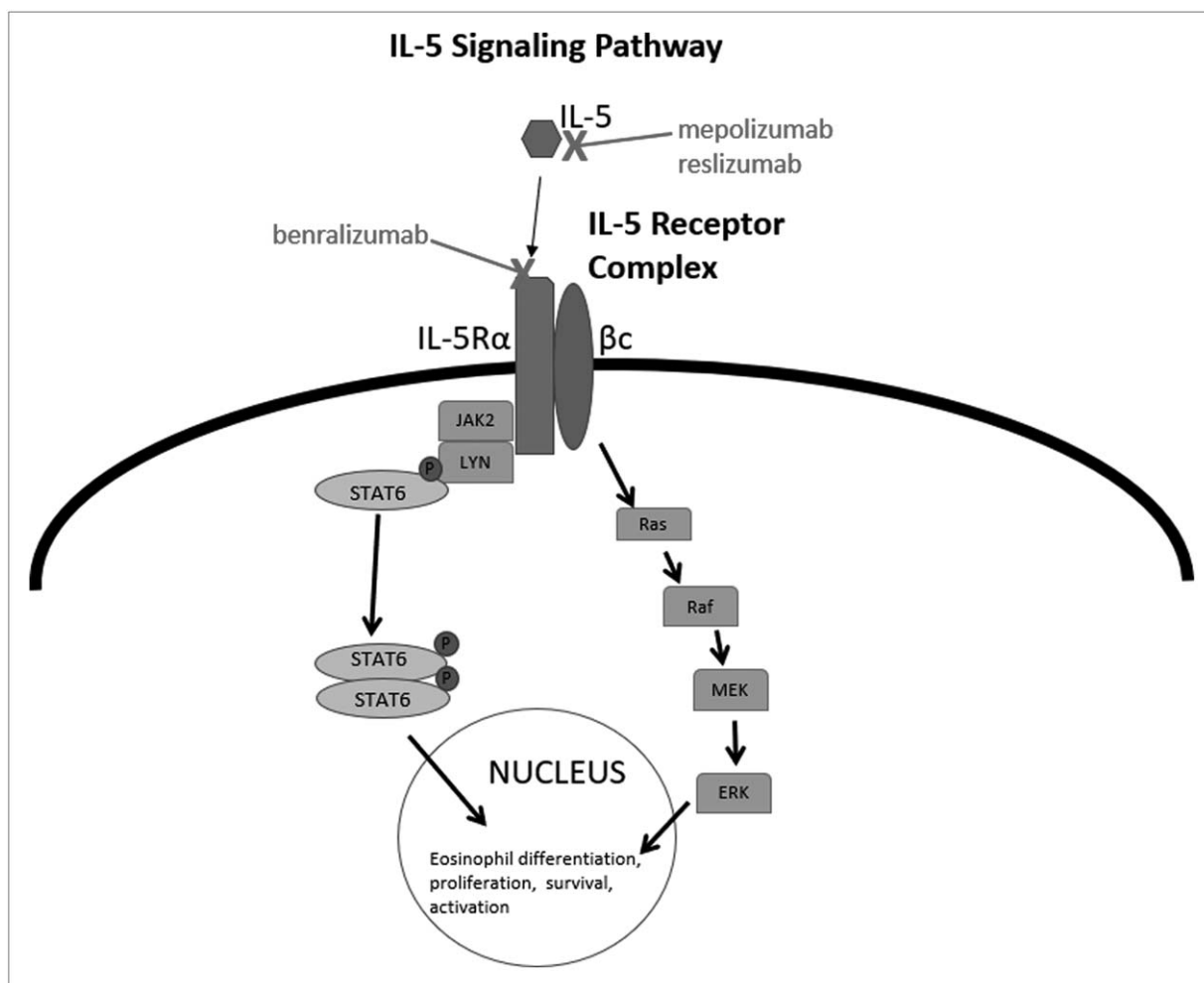


FIGURE 2. IL-5 binding to the IL-5 receptor complex (IL-5R α and β c) activates multiple kinases, including JAK2, Lyn and other signaling proteins, which signal through the Ras-Raf-MEK-ERK and JAK-STAT pathways to inhibit apoptosis and promote eosinophil survival, proliferation and activation. Mepolizumab and reslizumab are monoclonal antibodies against the IL-5 cytokine, whereas benralizumab is an anti-IL-5R α monoclonal antibody that prevents signaling through the IL-5 receptor.

Initial studies of mepolizumab, an anti-IL-5 mAb, failed to show clinical benefit in the overall asthmatic population, despite reducing numbers of sputum and blood eosinophils [35]. However, two subsequent mepolizumab trials in selected patients with elevated sputum eosinophils demonstrated a steroid-sparing effect, as well as improvements in asthma exacerbation rates and AQLQ scores [36,37]. The more recent DREAM and MENSA phase 3 trials further demonstrated improvements in asthma exacerbations in patients with blood eosinophil counts at least 150 cells/ μ l, and the SIRIUS study also demonstrated a steroid-sparing effect [38–40]. There was no improvement in FEV1, peak expiratory flow, airway hyper-responsiveness and AQLQ and ACQ scores. Mepolizumab has been successfully and safely utilized since receiving food and drug administration (FDA) approval in 2015 [41]. Reslizumab, an anti-IL-5 mAb administered intravenously, was

able to lower blood and sputum eosinophil counts and demonstrates improved FEV-1 and ACQ scores, as well as reductions in asthma exacerbation rates [42,43]. It has since received approval in asthmatic patients with eosinophil counts at least 400 cells/ μ l [44]. However, recent studies of fixed-dose, subcutaneous formulations of reslizumab administered to individuals with eosinophil counts more than 300 cells/ μ l failed to reduce asthma exacerbations or daily oral corticosteroid use [45,46].

Benralizumab, a humanized mAb that directly binds to the α subunit of the IL-5 receptor on eosinophils, exerts its effects with dual mechanisms of action [47]. Not only does it inhibit the binding of IL-5 to its receptor and prevent eosinophil activation and proliferation, but it also attracts natural killer cells and facilitates eosinophil clearance via antibody-dependent cell-mediated cytotoxicity. Multiple phase 3 studies, including six important

trials within the WINDWARD program, have demonstrated a marked steroid-sparing effect as well as significant improvements in asthma symptom control, lung function and asthma exacerbations. Furthermore, benralizumab effectively depleted sputum, peripheral, as well as bone marrow eosinophil counts. It has since received FDA approval for severe asthmatic patients with minimum eosinophil counts at least 150 cells/ μ l [48].

INHIBITION OF CYTOKINES VERSUS RECEPTORS

Whether mAb inhibition of cytokines or cytokine receptors provides greater clinical benefit has not been examined. Trials of several biologics targeting either IL-4 or IL-13 (e.g. pascolizumab, lebrikizumab and tralokinumab) have failed to demonstrate clinical benefit in asthmatic patients, whereas inhibition of the IL-4 receptor and downstream IL-4 and IL-13 pathways showed significant results [20–24]. Dupilumab was able to reduce maintenance oral steroid doses and improve FEV1 and asthma exacerbation rates, as well as AQLQ and ACQ scores compared to the placebo group [4^{***}–6^{***}]. It is likely that concurrent inhibition of both the IL-4 and IL-13 signaling pathways via blockage of a shared receptor has much greater impact than blockage of one pathway alone.

Selection of either anti-IL-5 or anti-IL-5 receptor therapies for eosinophilic asthma can be complicated as well. Although trials of mepolizumab, which targets the IL-5 cytokine, showed improvements in asthma exacerbation rates, there was little improvement in FEV1 and symptom control scores [38–40]. In contrast, inhibition of the IL-5 receptor with benralizumab had more profound clinical benefits, with significant improvements in asthma symptom control scores and FEV1, as well as rate of exacerbations [47]. Compared to IL-5 mAbs, benralizumab was able to demonstrate efficacy with a lower threshold eosinophil count and a longer duration of action requiring less frequent dosing. Although reslizumab, an anti-IL-5 mAb, demonstrated similar clinical efficacy with IV administration, it failed to show benefit with subcutaneous formulations [45^{*},46^{*}]. Taken together, it can be speculated that subcutaneous mAbs targeting cytokines may have difficulties pharmacokinetically and pharmacodynamically in fully neutralizing the large number of small, specific proteins in the vast cytokine milieu. Therapies that target a receptor and prevent signal transduction may be a more favorable option. A recent Glaxosmithkline-sponsored indirect comparison trial suggested that mepolizumab had greater clinical benefits compared with reslizumab and benralizumab [49^{*}]. Another indirect comparison using meta-analysis suggested

that reslizumab may be more efficacious than benralizumab [50^{*}]. Further research with direct comparison trials is needed to discern the biologic most convenient and clinically beneficial for a maximal number of patients.

CLINICAL BENEFITS OF INTERLEUKIN-4/ INTERLEUKIN-13 VERSUS INTERLEUKIN-5 INHIBITION

The eosinophil is arguably the most important inflammatory cell involved in the pathogenesis of asthma [51]. However, while its function as a final cytotoxic effector molecule in asthma pathogenesis makes it a prime target for anti-IL-5 biologic therapy, many other signaling proteins and molecular cascades play important roles in eosinophil activity and recruitment to the airway. Furthermore, because of the heterogeneous nature of inflammation in asthma populations, there is often an overlap of asthma phenotypes with varying degrees of eosinophil participation in each individual [52,53]. Disruption of the IL-4/IL-13 pathways may impair a larger plethora of signaling cascades involved in the primary clinical features of asthma, including airway inflammation and hyper-responsiveness, bronchoconstriction and mucous secretion. Despite lacking eosinophil-reducing ability, dupilumab showed benefit in the overall asthma patient population regardless of baseline eosinophil counts, and was also able to decrease levels of several inflammatory markers [4^{***}–6^{***}]. Whether selective inhibition of eosinophil proliferation and activity via the IL-5 pathway or disruption of a potentially broader Th2 inflammatory response via the IL-4/IL-13 is more clinically beneficial in severe asthmatic patients has not yet been examined.

CONCLUSION

Although a variety of biologic therapies targeting cytokines and cytokine receptors involved in Th2 inflammation have been developed for the treatment of severe asthma, there have been no direct comparison trials of the biologics. As subcutaneous mAbs targeting cytokine receptors demonstrated a broader range of clinical benefits compared to those directed against cytokines, inhibition of cytokine receptors may disrupt inflammatory signaling pathways more thoroughly with more robust results. In addition, the complexity of asthma pathogenesis makes it difficult to recognize the dominant molecular pathway whose inhibition would most benefit all asthmatics. Utilization of serum biomarkers currently provides a more personalized and precise method in the classification and clinical

management of individual asthma profiles. However, individuals can display biomarkers and clinical features characteristic of several asthma phenotypes, thus ruling them eligible for several biologics and making it difficult to predict their response to specific therapies. A biologic capable of reducing several validated biomarkers of type-2 inflammation in asthma while improving multiple clinically relevant endpoints would be ideal, and further research with independently funded, head-to-head trials of approved biologics is needed to elucidate a favorable therapeutic option.

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Conflicts of interest

The authors whose names are listed certify that they have no affiliations with or involvement in any organization or entity with any financial interest or nonfinancial interest in the subject matter or materials discussed in this article.

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