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Targeting thymic stromal lymphopoietin for the treatment of severe eosinophilic asthma

Abstract

Asthma is a heterogenous chronic inflammatory airway disease comprising of four phenotypes classified based on sputum cytology, which differ in immunopathophysiology, disease severity, and response to pharmacological therapy. The phenotypes of asthma include eosinophilic, neutrophilic, paucigranulocytic, and mixed cellularity. Eosinophilic asthma affects about 40-60% of all asthma cases. It is associated with atopy, eczema, allergic rhinitis, aspirin exacerbated respiratory disease, and chronic rhinosinusitis with nasal polyps. The airway epithelium plays an important role in initiating eosinophilic inflammation, and in the pathogenesis of eosinophilic asthma. Injured or damaged airway epithelium release three cytokines, such as interleukin-25 (IL-25, IL-33, and thymic stromal lymphopoietin (TSLP). Epithelial cytokines also known as alarmins act in concert and synergistically in promoting eosinophilic inflammation, airway hyperresponsiveness, and remodeling. Targeted inhibition of epithelial cytokines is an attractive and precise approach to treat eosinophilic asthma. There are no approved biologics targeting IL-25, and IL-33 for the treatment of eosinophilic asthma. Tezepelumab an anti-TSLP monoclonal antibody is the only anti-alarmin biologic approved for the treatment of severe asthma irrespective of the phenotype. It is effective in reducing the exacerbation rates, and improves lung function, and health related quality of life.

Keywords: eosinophilic asthma, alarmins, thymic stromal lymphopietin, tezepelumab

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Abbreviations: AHR, airway hyperresponsiveness; ASM, airway smooth muscle; COPD, chronic obstructive pulmonary disease; CRSwNP, chronic rhinosinusitis with nasal polyps; FDA, Food and Drug Administration; FeNO, fractional exhaled nitric oxide; HLQoL, health related quality of life; IgE, immunoglobulin E; IL, interleukin; ILC2, innate lymphoid group 2 cells; mAb, monoclonal antibody; R, receptor; SoC, standard of care; ST2, Suppression of immunogenicity 2; Th2, T helper 2 cells; TSLP, thymic stromal lymphopoietin

Introduction

Severe eosinophilic asthma

Asthma impacts a great health care burden and economical costs. It affects approximately 334 million people, and causes 250 million deaths each year worldwide. Its prevalence depends on genetic, environmental, and economical factors.[1,2] The prevalence has reached a plateau in high-income countries, but it is continuing to rise in low and middle-income countries.[3–5]

It is a heterogenous chronic inflammatory airway disease comprising of four phenotypes classified based on sputum cytology, which differ in immunopathophysiology, disease severity, and response to pharmacological therapy.[6] The phenotypes of asthma include eosinophilic, neutrophilic, paucigranulocytic, and mixed cellularity.[6–8] Of the four phenotypes neutrophilic asthma seems to be the most severe. It occurs mostly in adults, associated with several cormobidities, such as obesity, and gastroesophageal disease, and does not respond to biologics.[9]

Eosinophilic asthma occurs in about 50% to 60% of all cases of asthma,[10–13] and it is the most common phenotype in children presenting with acute asthma.[14] Similarly, about 40-60% of patient with severe, uncontrolled asthma have an eosinophilic phenotype.[10–13] It is associated with atopy, and diseases of the atopic match, and Samter's triad (Table 1).[15–18]

Table 1 Diseases associated with eosinophilic asthma

Atopic match	Samter's triad
Food allergy	Eosinophilic asthma
Allergic rhinitis	Aspirin exacerbated respiratory disease
Atopic dermatitis	CRSwNP
Allergic rhinitis	
Eosinophilic asthma	
Chronic rhinosinusitis with nasal polys (CRSwNP)	
Eosinophilic esophagitis	

The laboratory features of eosinophilic asthma include an elevated blood and sputum eosinophil count, and raised immunoglobulin E (IgE). The diagnostic biomarkers of eosinophilic asthma include elevated levels of fractional exhaled nitric oxide (FeNO), raised serum dipeptidyl peptidase-4, periostin, and osteopontin.[19–23] Biomarkers are very useful in stratifying patients for precision, personalized biotherapy, because patient with neutrophilic asthma do not respond to biologics.

The pathophysiological mechanism of eosinophilic asthma is chronic airway inflammation due to hypersecretion of cytokines by CD4+ T helper 2 (Th2) cells, innate lymphoid group 2 cell (ILC2), haemopoietic and non-haemopoietic cells, such as eosinophils, basophils, mast cells, epithelial cells, fibroblasts, myofibroblasts, and airway smooth muscle (ASM) cells. Activation of these cells lead to secretion of cytokines, such as interleukin-5 (IL-5), IL-4, IL-13, which result in airway hyperresponsiveness (AHR), and remodeling. The airway structural changes which include goblet cell hyperplasia and mucus production, subepithelial fibrosis, airway smooth muscle hyperplasia and hypertrophy, and neovascularization leads to severe airway obstruction, and severe asthma. Furthermore, the airway remodeling result in difficult asthma to control with the standard of care (SoC). Biologics which target the inciting interleukins, such mepolizumab (anti-IL-5),[24–26] reslizumab (anti-IL-5),[27,28] benralizumab (anti-IL-5R),[29–31] dupilumab (anti-IL-4Rα),[32,33] and tezepelumab

(anti-TSLP),[34,35] have been very successful in the treatment of severe eosinophilic asthma. They have been shown to decrease the rate of exacerbation, improve lung function, and health related quality of life (HRQoL). Additionally, they have been demonstrated to allow patients to taper or discontinue corticosteroids, which have numerous side effects.

Airway epithelial cells form the first line of defense against external insults, such as viral and bacterial infections, allergens, toxic particulate matter, noxious pollutants, and gases.[36] Airway epithelial cell injury and dysfunction plays an important role in sensitization to allergens, and in the pathogenesis of asthma.[37,38]

Injured or damaged epithelium in response to viral respiratory infections, allergens, pollutants, release three epithelial cytokines also known as "alarmins". The three alarmins belong to different families of cytokines but they act in concert and synergistically to perpetuate eosinophilic airway inflammation, and severe asthma. They include IL-25, IL-33, and thymic stromal lymphopoietin (TSLP).[39,40] Alarmin cytokines are favorable targets for the development of new biologics for the treatment asthma, because they are the initiators of eosinophilic inflammation. Notably, they stimulate production and secretion of Th2 cytokines, such as IL-5, IL-4, and IL-13.

There are no approved biologics targeting IL-25, and IL-33. Two IL-33 monoclonal antibodies (mAb), namely itepekimab, and etokimab had their clinical trial studies discontinued in phase 2 because of lack of efficacy compared to placebo. Astegolimab and tozorakimab are anti-ST2 and anti-IL-33 mAb, respectively are in phase 2 clinical trials.[41] Table 2 shows approved anti-alarmin biologics, and in development for the treatment of chronic airway diseases.

Table 2 Anti-alarmin biologics for the treatment of chronic airway diseases

Biologic	Mechanism of action	Asthma	COPD
Itepekimab	Anti-IL33	Discontinued	Phase 3
Etokimab	Anti-IL33	Discontinued	No trial
Tozorakimab	Anti-IL33	Phase 2	Phase 3
Astegolimab	Anti-ST	Phase 2b	Phase 2
Tezepelumab	Anti-TSLP	Approved 12/20/21	Phase 2b
Ecleralimab	Anti-TSLP	Phase 2	Phase 2

Currently, the only approved anti-alarmin biologic is tezepelumab (Tezspire). Tezspire is a first-in-class monoclonal antibody that blocks TSLP. It was approved by the U.S. Food and Drug Administration (FDA) on December 20, 2021 for the treatment of severe asthma without an eosinophilic phenotype in patients 12 years and older.[42] Treatment with tezepelumab has been shown to significantly reduce exacerbation rates, and biomarkers of inflammation, such as blood eosinophil count, and FeNO. Tezspire is effective in most asthma phenotypes, irrespective of eosinophil counts, and FeNO levels, which are biomarkers of eosinophilic asthma. It is safe and is well tolerated by patients.[43–46]

Recently, ecleralimab (CSJ117) a potent neutralizing antibody fragment directed against TSLP, formulated as PulmoSolTM engineered powder in hard capsule for delivery to the lung via a dry powder inhaler. Ecleralimab has been shown to significantly attenuates the early and late asthmatic responses, and reduced biomarkers of eosinophilic asthma.[47] If approved, it may be the first inhaler biologic for the treatment of severe asthma. Direct delivery of biologics to the airways is an innovative, and possibly an effective and safe way to treat severe asthma.

Conclusion

Injured or damaged epithelium in response to viral respiratory infections, allergens, pollutants, release three epithelial cytokines also known as "alarmins", including IL-25, IL-33, and TSLP. Alarmins play an initial central role in the pathogenesis of severe eosinophilic asthma. Targeting epithelial cytokines is an attractive approach to treat eosinophilic asthma.

There are no anti-IL-25, and anti-33 biologics approved for the treatment of eosinophilic asthma. Tezepelumab (Tezspire) is a first-in-class fully human IgG2λ monoclonal antibody that binds to TSLP, and prevents it to interact with its heterodimeric receptor TSLPR. Tezepelumab is the only anti-alarmin biologic approved by the FDA for the treatment of severe asthma irrespective of the phenotype. Advances in inhaler technology may allow pulmonary delivery of biologics, such as ecleralimab directly to the inflamed airways for the treatment of severe asthma.

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Conflicts 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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