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The Role of Alarmin Cytokines in the Pathogenesis and Treatment of Severe Uncontrolled Asthma

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Abstract

Asthma is a highly prevalent chronic airway disease, affecting more than 358 million individuals globally, and it is the most common chronic inflammatory respiratory disease in children. Approximately 10% of patients with asthma have severe uncontrolled disease, unresponsive to high-dose inhaled corticosteroids, and long-acting β-agonists. About 55% of patients with severe asthma have the eosinophilic phenotype. A smaller proportion of these patients respond favorably to monoclonal antibodies targeted at T helper type 2 Interleukins (IL), such as mepolizumab, reslizumab, benralizumab and dupilumab. Add-on biologics have been shown to reduce exacerbation rates, and improve asthma control, and lung function. However, the majority of patients with neutrophilic and other phenotypes of asthma do not respond to anti-eosinophilic asthma biologics. Epithelial "alarmin" cytokines, IL-25, IL-33, and Thymic Stromal Lymphopoietin (TSLP) seem attractive to inhibit, because they are upstream initiator cytokines. TSLP plays a key role in the pathophysiology of eosinophilic asthma, neutrophilic asthma, and airway remodeling. Tezepelumab is a first-in-class fully human IgGʎ2 mAb that bind to TSLP, and prevents it to interact with its receptor TSLPR, thus inhibiting multiple downstream immune pathways, and production of cytokines, and chemokines. Tezepelumab has been shown to attenuate the early and late asthmatic responses, reduce exacerbation rates by 71%, and to decrease biomarkers of eosinophilic inflammation (blood eosinophil counts, and Fractional Exhaled Nitric Oxide, [FeNO], IL-5, IL-13). The improvements were observed in all the phenotypes of asthma, and independent of baseline blood eosinophil counts, IgE levels, and FeNO concentration. Thus, targeting alarmin cytokines is a charismatic approach to treat severe uncontrolled asthma.

Keywords: Severe asthma; "Alarmin cytokines"; Thymic stromal lymphopoietin; Tezepelumab

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Introduction

Asthma is a highly prevalent chronic airway disease, affecting more than 358 million individuals globally, and it is the most common chronic inflammatory respiratory disease in children [1,2]. Asthma has been classified cytologically depending on the predominant leukocyte count in induced sputum, and biomarkers of airway inflammation into eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic phenotypes [3,4]. Approximately 3.6% to 10% of patients with asthma have severe refractory disease, which is uncontrolled despite treatment with high-dose Inhaled Corticosteroids (ICS), Long Acting β2-Agonists (LABA), and/or Leukotriene Receptor Antagonists (LTRA) [5,6]. Approximately 40% to 60% of patients with severe asthma have the eosinophilic phenotype, and eosinophilic asthma is the most common phenotype in children with severe acute asthma [7-12]. T helper 2 lymphocytes (Th2) cytokines, such as Interleukin-5, (IL-5), IL-4, IL-13, IL-25, IL-33, and Thymic Stromal Lymphopoietin (TSLP) play a key role in the pathophysiology of eosinophilic asthma [13-16]. The immunopathological mechanisms of IL-5, IL-4, and IL-13 in the pathogenesis of asthma have been well established, and have led to the discovery and development of very effective biotherapeutics for the treatment of severe uncontrolled eosinophilic asthma [17-20]. However, the pathophysiological mechanisms of the "alarmin" cytokines (IL-25, IL-33, and TSLP) in the pathogenesis of different phenotypes of asthma are incompletely understood. Interleukin-25, IL-33, and TSLP are epithelial-derived cytokines secreted by epithelial cells in response to allergens, viral respiratory infections, pollutants, environmental tobacco smoke, and physical injury [21-23]. They are upstream and initiator cytokines which play a leading role in the pathogenesis of Th2-driven eosinophilic asthma, and participate in neutrophilic airway inflammation [24-28]. Furthermore, IL-25, IL-33, and TSLP play a central role in the development of Epithelial-Mesenchymal Trophic Unit (EMTU), which orchestrates airway inflammation and remodeling, leading to lung structural changes, and fixed airflow obstruction [29-32]. Alarmin

cytokines may contribute to the progressive decline in lung function, and corticosteroid-resistant asthma. Currently, there is only one anti-alarmin biologic (tezepelumab) which has been approved by the US Food and Drug Administration (FDA) for the treatment of severe uncontrolled asthma without an eosinophilic phenotype in patients 18 years and above [33]. Targeting the upstream alarmin cytokines seems very attractive in the development of novel biologics for the treatment of severe asthma, particularly due to allergens, pollutants, and respiratory viral-induced asthma exacerbations [34,35].

Interleukin-25

Interleukin-25 (IL-25) also known as Interleukin-17E (IL-17E) is a pro-inflammatory cytokine belonging to the Interleukin-17 family, and was first identified by Lee and colleagues in 2001 [36]. Human IL-25 has a molecular weight of 16.7 kDa, and comprised of 161 amino acid residues. The interleukin-17 family has six cytokines designated Il-17A, IL-17B, IL-17C, IL-17D, IL-17E, and IL-17F, and five receptor complexes, IL-17RA-IL-17E [37]. Unlike other family members, such as IL-17A, and IL-17F, IL-25 is predominantly responsible for propagating Th2 cytokine-driven allergic responses, and pathophysiology of eosinophilic asthma [38,39]. Conversely, IL-17A (hereafter referred as IL-17) is responsible for Th17-driven immune responses, and the pathogenesis of neutrophilic asthma, and other autoimmune diseases, such as psoriasis, rheumatoid arthritis, and inflammatory bowel disease [40]. Interleukin-25 is produced mainly by epithelial cells in response to allergen proteases, pollutants, and viral respiratory infections, such as rhinovirus, and respiratory syncytial virus [41-43]. It is also produced by Th2 cells, which were the earliest recognized source of IL-25 [44]. Other sources of IL-25 include innate Lymphoid Cells Group 2 (ILC2), Eosinophils, Basophiles, and mast cells [45,46]. IL-25 plays an important role in activating eosinophils, through activation of adhesion molecule ICAM-1, and promotes eosinophil survival by preventing apoptosis. It promotes recruitment of Th2 cells, ILC2, B cells, eosinophils and mast cells to the site of allergic inflammation in the lung. This results in production of Immunoglobulin E (IgE) by B cells, airway eosinophilia, airway hyperresponsiveness, and remodeling [40,47]. Furthermore, IL-25 stimulates several immune cells, such as Th2 cells, ILC2, eosinophils, and mast cells, and structural cells, including endothelial cells, epithelial cells, and fibroblasts to produce and secrete pro-inflammatory cytokines (IL-4, IL-5, IL-6, IL-8, Il-9, and IL-13), and chemokines, namely CXCL8, and macrophage inflammatory protein-1 [36,41,47-50]. Epithelial IL-25 can act *via* an autocrine feed forward mechanism to produce more IL-25, as well as other potent "alarmin" cytokines, including IL-33, and TSLP, thus amplifying the allergic responses [51,52]. Interleukin-25 signals through a heterodimeric receptor complex (IL-25R) consisting of IL-17RA subunit (the signaling subunit), and IL-17RB, which is specific for IL-25 [53]. Both receptor subunits contain a conserved SEFIR domain at the cytoplasmic region [54,55]. Binding of IL-25 to its receptor complex leads to recruitment of the adaptor molecule Ac1 through the homotypic interactions of the SEFIR domains, which also is present on Ac1 [56,57]. Ac1 on epithelial cells, Th2 cells, ILC2, and other immune cells, plays a critical role in Il-25 signaling, and the production of several cytokines and chemokines responsible for Th2-allergic responses [56,58]. In another pathway, IL-25 activates MAP kinases, such as p38, JNK, and NF-κB which stimulates downstream signaling pathways [59]. Wu et al. have reported IL-25 signaling involving activation of STAT5 in cooperation with GATA-3 [60]. This pathway is critical for the induction of Th2 cells, and epithelial cells to produce cytokines and chemokines [61,62]. However, the exact mechanisms of the downstream signaling pathways have not been fully understood. Nonetheless, the final result is the induction of a plethora of cytokines and chemokines from immune cells, and airway structural cells, and the pathophysiology of eosinophilic asthma. Patients with mild allergic asthma have significantly increased expression of IL-17RA and IL-17RB on mature eosinophils, and higher levels of IL-25 compared with a topic non-asthmatics, and non-atopic normal subjects [63]. Additionally, asthmatic patients with higher levels of IL-25 messenger RNA have greater airway hyperresponsiveness to allergen challenges, increased serum IgE levels, and airway and blood eosinophil counts, and has good response to ICS compared with asthmatics with low IL-25 expression [64]. They have also more pronounced subepithelial thickening, and fibrosis compared with healthy controls, which is a marker of Th2 cytokine-induced inflammation, especially Il-4, IL-13, and IL-25 [64]. Moreover, IL-25 has been shown to act directly on human fibroblasts inducing collagen secretion, and blockade of IL-25 inhibited, mesenchymal cell proliferation, subepithelial fibrosis, and AHR [65]. IL-25 also promotes Airway Smooth Muscle (ASM) cell hyperplasia, and collagen deposition around the airways, thickening the airway wall, which supports its involvement in airway remodeling [66]. Furthermore, Corrigan et al. [67] have shown that IL-25 contributes to angiogenesis, through increases in endothelial cell VEGF/VEGF receptor expression *via* the PI3/Akt and Erk/MAPK pathways. Neovascularization could lead to expansion of the bronchial vasculature, airway edema, and airway narrowing. Tang et al. [68] have reported that, IL-25 high affinity receptor, IL-17RB expression on eosinophil-lineage committed progenitor cells (EoP) is increased in peripheral blood of subjects with asthma after allergen challenges. This may suggest that the increase in IL-25, and its receptor subunits may contribute to the recruitment of eosinophils from the bone marrow, and circulation to the allergic airways, thus further increasing airway eosinophilic inflammation [68]. IL-25 and its heterodimeric receptor are attractive targets for new drug discovery for the treatment of Th2-driven eosinophilic asthma. Currently, there are no anti-IL-25 biotherapeutics which have reached the primary endpoints in the treatment of asthma, including brodalumab, a human anti-IL17Ra mAb, which partially inhibits IL-25 activity by binding to the IL-17RA subunit [34]. Busse et al. [69] observed no overall treatment differences in terms of Asthma Control Questionnaire (ACQ) scores, and lung function in the brodalumab treated patients (n=226) compared with placebo (n=302).

Interleukin-33

Intereleukin-33 (IL-33) is the 11th member of the Interleukin-1 (IL-1) family of cytokines. It was first identified as a nuclear factor of high endothelial venules and termed NF-HEV in 2003, and later identified to belong to the IL-1 family, which also include IL-1α, IL-1β, and IL-18 [70,71]. It resides exclusively in the nucleus of structural cells, but also in the cytoplasm, and extracellular compartment where it promotes various biological effects. IL-33 is mainly involved in initiating and propagating Th2 immune responses via effects on Th2 cells, ILC2, dendritic cells, CD4+ cells, eosinophils, and mast cells [70]. The molecular structure of IL-33 consists of an N-terminal nuclear localizing signal, a helix-turn-helix motif, and a C-terminal region, which has structural homology to the IL-1 cytokine family [71]. The full-length form, pro-interleukin-33 is localized in the nucleus, but the function of interleukin in the nucleus is still under speculation. Interleukin-33 is released after necrosis, cell damage, or mechanical

stress, and acts as an "alarmin" cytokine to elicit a protective immune response. During necrosis, IL-33 remains in its active biological form; however, in apoptotic conditions, it is cleaved to its inactive forms by caspase 3 and caspase 7 [72]. IL-33 signaling is through a heterodimeric receptor complex comprising interleukin-1 receptor like 1 (IL1RL1 also known as ST2), and IL-1R accessory protein (IL-1RAcP). IL-33 binds to its receptor complex, and recruit's adaptor proteins, such as the myeloid differentiation factor 88 (My88) adaptor protein. The next molecular signaling includes the recruitment of IL-1R-Associated Kinase 1 (IRAK1). This results in the activation of different signaling downstream pathways, including Mitogen-Activated Protein Kinases (MAPK), and Nuclear Factor-KappaB (NF-kB), *via* TNF receptor-associated factor 6 (TRAF6) [70,71]. In another pathway, IL-33 increases phosphorylation of extracellular signal-regulated Kinase (ERK1/2)/c-Jun N-terminal Kinase (JNK1/2)-Activator Protein-1 (AP-1), JAK2, and SKY [70,73,74]. The final pathways lead to induction and release of cytokines, chemokines, and growth factors by several types of immune cells. Il-33 receptor complex is constitutively expressed in several types of cells, such as endothelial cells, epithelial cells lining the airways, and the gastrointestinal system, smooth muscles cells, and adipocytes [70,71,75-77]. It activates several immune cells, including Th2 cells, ILC2, NK cells, B cells, eosinophils, basophiles, and mast cells, and structural cells, such as endothelial cells, epithelial cell, and fibroblasts [70,71]. Activation of these cells propagate Th2 immunological responses and the secretion of a myriad cytokines, and chemokines [70,76]. IL-33 activates a dendritic cell which in turn promotes T cell differentiation, and Th2 polarization, thus increasing Th2 cell pool for the secretion of pro-inflammatory cytokines [78]. IL-33 is able to induce T cell proliferation, and is capable of stimulating Th2 cells to produce large quantities of IL-5, and IL-13 [79]. ILC2 differentially express c-kit (CD117) and receptors for IL-25 (IL-17Rβ), and IL-33 (T1/ST2). Co-stimulation of IL-33 with IL-2, IL-7 or TSLP results in greatly enhanced production of IL-5, and IL-13 by ILC2 [80]. IL-33 also stimulates B1 cell proliferation, and promotes CD8+ T cell responses, and thus, additionally induces Th1 immune responses [81-83]. IL-33 has been reported to enhance basophile degranulation, and promotes eotaxin mediated basophile migration to allergic airways [84]. IL-33 potently activates and stimulates maturation of mast cells to produce several cytokines (IL-1β, IL-5, IL-8, IL-13, and TNF-α), chemokines, such as CCL1, and CXCL8 (IL-8), and growth factors (GM-CSF) through activation of TN-κB pathway [85]. Additionally, IL-33 prolongs survival of cultured mast cells derived from cord blood by promoting cell adhesion. It can also act in concert with TSLP to further enhance secretion of cytokines and chemokines by mast cells [86]. Human eosinophils express both ST2 RNA and protein [87]. IL-33 has been shown to activate eosinophils, independently of IL-3, IL-5, and GM-CSF. It is capable of stimulating eosinophils to produce and release cytokines and chemokines, such as CXCL8/IL-8, and CCL2/MCP-1, through ST2 activation [87]. It also prolongs eosinophil survival, adhesion, migration, and degranulation to produce superoxide's [87-90].

There is compelling evidence that IL-33 is associated with the pathophysiology of airway remodeling, and severe asthma [91]. Bianchetti et al. [92] have shown that circulating fibrocytes from patients with allergic asthma expressed higher levels of ST2 receptor compared to those from healthy controls. Recombinant human IL-33 has also been shown to induce both proliferation and migration of fibrocytes to lung tissue [92]. Saglani et al. have reported that IL-33 promotes collagen synthesis in fibroblasts from asthmatic children, and is associated with increased thickness of the reticular basement membrane in bronchial biopsy specimens from children with steroid-resistant asthma [93]. An et al. [94] have demonstrated airway collagen deposition and metalloproteinase expression in murine surrogate of asthma after intranasal administration of house dust mite in mice [94]. Experimental studies have shown that IL-33 is secreted in large amounts in response to allergen challenge, and IL-33 RNA is highly expressed in human bronchial, and IL-33 and ST2 genes and protein are significantly elevated in induced sputum of patients with moderate asthma compared with patient with mild asthma [95]. Increased level of soluble ST2 protein in sera has also been associated with acute asthma exacerbations [96]. Elevated expression of IL-33 and TSLP in the airways of asthmatic patients is associated with severe refractory asthma and low FEV1 [97]. Similarly, Prefontaine et al. [98] have shown that the expression of IL-33 is significantly increased in the bronchial epithelial cell of patients with asthma compared with healthy individuals. IL-33 plays a major role in the pathophysiology of AHR, airway remodeling, and severe eosinophilic asthma. Targeting this cytokine systemically or topically has potential for future treatment and prophylaxis of eosinophilic asthma, particularly due to viral-induced asthma exacerbations. Currently, there are no anti-IL-33 biologics which have reached endpoints in the clinical trials for the treatment of asthma.

Thymic Stromal Lymphopoietin

Thymic Stromal Lymphopoietin (TSLP) is an epithelial derived cytokine that belongs to type 1 cytokine group, which is part of the interleukin-2 cytokine family, comprising of IL-2, IL-4, IL-5, IL-7, IL-9, IL-13, and IL-21 [99]. It was first discovered in 1994 in the supernatant of a murine stromal cells, which had the capacity to support the growth of pre-B cell line [100].

The human TSLP gene is located on chromosome 5q22.1, next to other IL-2 family member's clusters, including IL-4, IL-5, IL-7, and IL-13 [101]. Several genome-wide associated studies have shown association between asthma and Single-Nucleotide Polymorphisms (SNPs) in the TSLP gene [102-104]. The likely causal polymorphism for allergy, asthma, and nasal allergy is rs1837253, which also directly regulates TSLP secretion [105]. TSLP is released from airway epithelial cells, following environmental insults, such as allergen proteases, respiratory viral and bacterial infections, chemical irritants, pollutants, and mechanical stress [106-110]. TSLP is also produced and secreted by keratinocytes, and gastrointestinal epithelial cells, Airway Smooth Muscle (ASM) cells, and immune cells such as dendritic cells, basophiles, eosinophils, and mast cells [111-119]. TSLP signals through a heterodimeric receptor TSLP-R consisting of a TSLP-binding α chain (TSLP-α), and an IL-7Rα subunit [120]. Downstream signal transduction of the TSLP receptor is via activation of Janus Kinase (JAK) 1, and Signal Transducer and Activator of Transcription (STAT) 1, 3, 4, 5 and 6, leading to activation of immune and structural cells to produce and secrete of cytokines and chemokines [120]. Its biological effects are mainly on dendritic cells, and mast cells, but it activates several cell types such eosinophils, basophiles, mast cells, and ASM cells to produce pro-inflammatory cytokines, and chemokines [106]. TSLP activates dendritic cells to up regulate the co-stimulatory molecules OX40, CD40, and CD80 that facilitate polarization of naïve CD4+ T cells to a Th2 phenotype, which secrete Th2 cytokine, and chemokines [121-123]. Therefore, TSLP, indirect promotes Th2 immune responses [121-124]. TSLP

has been reported to activate ILC2 to produce large amounts of IL-5, and Il-13 which orchestrate eosinophilic airway inflammation, AHR, and airway remodeling [125]. TSLP in concert with IL-1β, and TNF-α stimulates mast cells to produce Th2 cytokines, and chemokines (CXCL8, and CCL1) [106,126,127]. Mast cells following IgE cross-linking collaborate with ASM cells to produce large amounts of TSLP, which act in a feed-forward autocrine fashion to stimulate production of more cytokines, and chemokines [128,129]. Additionally, TSLP activates basophiles to produce Th2 cytokines, histamine, and promotes eotaxin-induced chemotactic responses of immune cells in the airways [130]. TSLP has been reported to drive local differentiation of Eosinophil Progenitor cells (EoPs) within the airways, migration and activation of EoPs to secrete cytokines, and chemokines [131,132]. Furthermore, TSLP protects eosinophil from apoptosis, and stimulates eosinophils to produce IL-6, eosinophil-derived neurotoxin, and chemokines, including CXCL8, CXCL1, and CCL2 [133,134]. The immune responses of TSLP on eosinophils are mediated through ERK, p38 MAPK, and NF-kB signaling pathway [133,134]. TSLP is a key mediator of interactions between immune cells and structural cells in the airways. It stimulates ASM cells migration, and mediates crosstalk between ASM cells and mast cells which infiltrate the muscle bundles of asthmatic airways. This leads to the production of cytokines, and chemokines by both cell types [126,135,136]. TSLP also stimulates lung fibroblasts to produce collagen, through a p38-MAPK-and STAT3-dependent pathway, which further amplifies airway remodeling [137,138]. Several studies have shown that TSLP expression is significantly elevated in patients with asthma compared with levels in healthy individuals in samples of serum, induced sputum, exhaled breath condensate, and BAL fluid [139-144]. Similarly, TSLP immunoreactive expression is increased in the inner and outer epithelial layers of the airways in bronchial biopsy specimens [143,145-148]. Notably, the level of TSLP expression in patients with asthma has been shown to correlate with the degree of airway obstruction and disease severity [143-145,148,149]. TSLP may contribute to airway remodeling in asthma, characterized by AHR, goblet cell and submucous glands hyperplasia and oversecretion of mucus, and subepithelial fibrosis [150]. This may lead to progressive decline in lung function, and poor response to corticosteroids, and to some of the biologics. TSLP seems attractive to target in therapeutic interventions to treat asthma because it is an upstream cytokine at epithelial barrier. It plays a central role in the pathophysiology of both eosinophilic and neutrophilic asthma, and paucigranulocytic asthma through its effects on airway remodeling.

Targeting Alarmin Cytokines

Currently, there are no anti-IL-25, and anti-33 biologics approved for the treatment of severe uncontrolled asthma. Tezepelumab is the only marketed anti-TSLP biotherapeutic, but other anti-TSLP biologics are in the pipeline.

Tezepelumab

Tezepelumab is a first-in-class fully human IgGλ2 Monoclonal Antibody (mAb) that binds to TSLP, and prevents it to interact with its receptor TSLPR, thus inhibiting multiple downstream immunopathologic pathways, and production of cytokines, and chemokines [151]. Phase 1b, Phase 2b PATHWAY, and Phase 3 clinical trials have documented the efficacy, and safety profile of tezepelumab in the treatment of in patients with uncontrolled asthma [152-154]. The first Phase I b clinical trial evaluated the efficacy of tezepelumab in an allergen challenge model of asthma in patients with mild, allergic asthma [152]. Tezepelumab 200 mg administered intravenously every 4 weeks for 3 months resulted in a decrease in blood eosinophil count at 2 weeks of treatment, and the levels of Fractional exhaled Nitric Oxide (FeNO) improved after the first dose of tezepelumab. Bronchoprovocation with allergen at day 42 and 84 showed that tezepelumab treatment significantly inhibited the early and late asthmatic responses [152]. Phase 2b PATHWAY, multicenter, randomized, parallel-group, double-blind, placebo-controlled trial assessed the efficacy of tezepelumab as add-on therapy in patients with moderate-to-severe asthma with a history of exacerbations, and uncontrolled disease [153]. This dose-ranging study demonstrated that tezepelumab significantly reduced exacerbation rates by 62% (70 mg every 4 weeks), 71% (210 mg every 4 weeks), and 66% (280 mg every 4 weeks); respectively compared with placebo. There was also improvement in lung function, and biomarkers of eosinophilic asthma (blood eosinophil count, and FeNO) in all the three treated groups. The improvements were observed in all the phenotypes of asthma, and independent of baseline blood eosinophil counts, IgE levels, and FeNO concentration [153]. This indicates that tezepelumab is effective in most phenotypes of asthma, which gives it an advantage [154]. The Phase 3 follow-up analysis of data of pro-inflammatory biomarkers and proteomics for patients who received tezepelumab 210 mg every 4 weeks showed that tezepelumab decreased serum IL-5 and IL-13 by 30% at 1 year, FeNO by 25%, and total serum IgE by 20% [155]. This indicates that treatment with tezepelumab can result in reduction in biomarkers of airway eosinophilia, and that tezepelumab is efficacious as an add-on treatment for patients with severe eosinophilic asthma. The NAVIGATOR trial [NCT03347279] investigating the safety and oral corticosteroid sparing potential of tezepelumab, met its endpoints. Tezepelumab added to Standard of Care (SoC) demonstrated a statistically significant clinically meaningful reduction in Annualized Asthma Exacerbation Rates (AAER) over 52 weeks in the overall patients' studies, compared with placebo when added on to SoC [156-158]. Most recently, Gauvreau et al. [159] have shown that CSJ117, a fully human neutralizing antibody antigen-binding fragment (Fab) that belongs to IgG1 isotype subclass attenuated both the Early Asthmatic Response (EAR) and Late Asthmatic Response (LAR) in 28 patients with mild, atopic asthma at day 84 of the study. CSJ117 was associated with significantly higher minimum FEV1 during the LAR on day 84 (P=0.038), and the percentage decrease and maximum decrease in FEV1 from before the allergen inhalation challenge were significantly less in the CSJ117 group compared with placebo (4.20% *vs.* 11.38%, P=0.008, and 9.28% *vs.* 17.70%, P=0.29); respectively [159]. Similarly, during the EAR, both measures were significantly less in the CSJ117 treated group compared with placebo. The aforementioned study was also associated with a reduction in FeNO, a biomarker of IL-13-driven eosinophilic inflammation, and none of the patient's withdrawal from the study due to adverse events [159]. CSJ117 probably might be the first inhaled biologic for the treatment of patients with asthma, especially when administered together with Single Maintenance and Reliever Therapy (SMART) with low-dose ICS-formoterol therapy.

Conclusion

Asthma is a heterogeneous chronic airway disease with different phenotypes which vary considerably in response to the standard of care therapy. Severe asthma is difficult to treat despite advances in the development of novel biotherapeutics to treat the disease. Biologics targeting the Th2-driven eosinophilic asthma are well established treatment for eosinophilic asthma, and have been shown to be safe

and very effective in the treatment of severe uncontrolled disease. However, there are no approved biologics for the treatment of other phenotypes of asthma. Tezepelumab an anti-TSLP antagonist has been demonstrated to be effective in the treatment of patients with both eosinophilic and neutrophilic asthma. The new kid in the biologics armament CSJ117 may prove to be effective as add-on inhaler treatment for patients with mild asthma, particularly when added to Single Maintenance and Reliever Therapy (SMART) with low-dose ICS-formoterol therapy.

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