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Editorial

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Targeting Alarmin Cytokines in the treatment of severe Asthma

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Editorial

Asthma is a heterogeneous chronic airway disease with distinct phenotypes, characterized by different immunopathological pathways, clinical features, disease severity, physiology, and response to treatment. The established cytologic phenotypes of asthma include eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic phenotypes [1]. Despite recent advances in the diagnosis and treatment of asthma, some phenotypes of asthma are difficult treat, and still pose an exceptionable health, and pharmaco-economic burden [2]. Approximately 3.6-10% 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) [3,4]. A smaller proportion of patients unresponsive to high-dose ICS, respond favourably to interleukin (IL) antagonists, such as mepolizumab and reslizumab (anti-IL-5), benralizumab (anti-IL-5Rα), and dupilumab (anti-4Rα). T helper type (Th2) targeted monoclonal antibodies (mAb) are highly effective in the treatment of eosinophilic asthma and have a good safety profile [5-8]. They reduce exacerbation, improve lung function (forced expired volume in 1 sec., FEV1), and the quality of life, and are steroid sparing [5-8]. However, they are mostly effective in patients with biomarker specific eosinophilic asthma, and have little therapeutic value in patients with other phenotypes of asthma, such as Th17-driven neutrophilic asthma, and paucigranulocytic asthma [9]. Biologics also do not ameliorate airway remodeling due to globlet cell hyperplasia and oversecretion of mucus, subepithelial basement thickening and fibrosis, airway smooth muscle (ASM) cell hyperplasia and hypertrophy [10-14]. Moreover, anti-Th2 biologic therapies decrease exacerbation rates by 48-59%.

There are no biologics targeting the Th17/IL-17 axis which play a pivotal role in the pathogenesis of neutrophilic asthma, one of the phenotypes of asthma unresponsive to biologics [9]. Busse at al. [15] in a randomized, placebo-controlled phase IIa trial of brodalumab, a monoclonal antibody against IL-17 receptor (IL-17Rα), in patients with moderate-to-severe asthma, reported no statistically significant benefit in terms of Asthma Control Questionnaire-6 (ACQ-6) scores, FEV1, or use of rescue short-acting β-agonists (SABA). O'Byrne and colleagues [16] in a larger, multicenter, dose finding trial, investigated AZD5069, a selective prostaglandin D2 receptor CXCR2 antagonist, in patients with uncontrolled asthma receiving medium-to-high dose ICS, and LABA. The findings in this clinical trial showed no significant benefits in the rates of exacerbations, ACQ-5, and FEV1. Risankizumab a humanised IgG monoclonal antibody that targets the p19 subunit of IL-23 is in phase 2 clinical trials for the treatment of asthma [17]. However, blockade of IL-17 and IL-17R is more effective in the treatment of other chronic autoimmune diseases, such as psoriasis vulgaris, erythrodermic psoriasis, psoriatic arthritis, and inflammatory bowel disease [17]. Brodalumab (Siliq®) [18], secukinumab (Cosenyx®) [19], and risankizumab (Skyrizi®) [20] have been approved in several countries, and are excellent drugs for the treatment of plaque psoriasis.

Airway epithelium constitutes the first line of defense against allergens, chemicals, pollutants, and microbes, such as viruses, bacteria, and fungal spores, and trauma in the atmospheric environment [21,22]. This can lead to epithelial injury, and impaired epithelial barrier function. Dysfunctional allergic epithelium in response to allergens, pollutants, and viral respiratory infections release three bioactive cytokines nicknamed "alarmins", including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) [23-27]. The three "whistle blower" cytokines, although they belong to different cytokine families, play synergistic roles in the pathophysiology of severe asthma [27]. They stimulate Th2, innate lymphoid group 2 cells (ILC2), mast cells, basophils, and oesinophils to release large quantities of cytokines (IL-4, IL-5, IL-13, IL-25, IL-33, TSLP), chemokines (eotaxins 1-3, CXCL8, CXCL9, CXCL10, CXCL11, CXCL12, CCL17, CCL22), and growth factors (TGF-β1, EGF-1, FGF, SCF, VEGF, angiogenin) responsible for airway hyperresponsiveness (AHR), and structural changes in the airways. Alarmin cytokines together with the pro-fibrotic Th2 cytokines IL-4 and IL-13 orchestrate airway remodeling, characterized by mucus hypersecretion, subepithelial fibrosis, increase in ASM mass and contractility, and progressive persistent airflow obstruction [28-30]. IL-25, IL-33, and TSLP are favourable targets for the development of new biologics for ads on treatment, and for prophylaxis of asthma, particularly due to asthma exacerbations provoked by respiratory viral infections [31].

Currently, there is no anti-IL-25, and anti-33 biologics approved for the treatment of asthma, including the eosinophilic phenotype. Tezepelumab a first-in-class monoclonal antibody that blocks TSLP is approved by the U.S. Food and Drug Administration (FDA) for the treatment of severe asthma without an eosinophilic phenotype in patients 18 years and older [32].

Thymic stromal lymphopoietin is a member of the 4-helix bundle cytokine, most closely related to IL-7 [33]. TSLP signaling pathway is mediated through its complex heterodimeric receptor formed by a TSLP-specific TSLPR subunit (CRLF2) and the IL-7α signaling chain [34,35]. TSLP activates dendritic cells in response to allergen exposure, inducing naïve CD4+ T cell differentiation to Th2 cells, which produce and secret cytokines (IL-4, IL-5, IL-9, and IL-13), chemokines, and growth factors [36,37]. This leads to switching of B cells to produce IgE, degranulation of mast cells, and eosinophils, and airway eosinophilia. TSSLP can also activate innate lymphoid group 2 cells (ILC2) to produce large amounts of IL-5, and IL-13 which drives Th2 immune responses [38]. There is

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evidence that that TSLP also plays a central role in the pathogenesis of Th17-driven neutrophilic asthma. TSLP promotes dendritic cells to induce polarization of naïve CD4+ T cells into Th17 cells which produce IL-17 a master cytokine responsible for neutrophilic asthma [39,40].

TSLP contributes to airway remodeling by stimulating ASM cell proliferation and migration [41,42], and facilitates crosstalk between ASM cells and mast cells [43]. This leads to secretion of more pro-inflammatory cytokines and chemokines by both cell types [44-46]. Additionally, TSLP stimulates fibroblasts to produce collagen which promotes reticular basement membrane fibrosis [47,48]. Thus TSLP plays a critical role in airway remodeling and fixed airflow limitation.

TSLP seems attractive to target in therapeutic interventions to treat asthma because it is an upstream cytokine at epithelial barrier, and it promotes both eosinophilic and neurophilic asthma, and paucigranulocytic asthma through its effects on airway remodeling [49].

Phase 1b [50], Phase 2b PATHWAY [51], and Phase 3 [52] clinical trials have documented the efficacy, safety profile of tezepilumab in the treatment of in patients with uncontrolled asthma. The first Phase Ib clinical trial evaluated the efficacy of tezepelumab in an allergen challenge model of asthma in patients with mild, allergic asthma [50]. 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 level 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 [50]. Phase 2b PATHWAY, multicentre, randomized, parallel-group, double-blind, placebo-controlled trial assessed the efficacy of tezepelumab as add-on therapy in patients with moderate-to-severe asthma and a history of exacerbations, and uncontrolled disease [51]. 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 [51]. This indicates that tezepelumab is effective in most phenotypes of asthma, which gives it an advantage [53]. 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% [54]. This indicates that tezepelumab is an effective biotherapeutic in the treatment of eosinophilic asthma.

Most recently, Gauvreau et al. [54] 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 [54]. Similarly, during the EAR, both measures significantly less in the CSJ117 treated group compared with placebo. CSJ probably might be the first inhaled biologic for add on treatment for patients with asthma. 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.

In summary, biologics targeting the Th2-driven eosinophilic asthma are well established treatment for severe steroid unresponsive asthma, and have been shown to be safe and very effective in the treatment of severe uncontrolled disease. 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 and well tolerated as add on treatment for patients with mild asthma.

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