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The role of interleukin-33 in the pathogenesis, and treatment of severe asthma

Abstract

Interleukin-33 (IL-33) belongs to the IL-1 family of cytokines, which has 11 members, including IL-1α, IL-1β, IL-1Ra, IL-18, IL-36α, IL-36β, and IL-37. Unlike its family members, IL-33 mediates T helper type-2 (Th2) immune responses, and promotes eosinophilic inflammation, similar to the other epithelial-derived cytokines, such as IL-25, and thymic stromal lymphopoietin (TSLP). Epithelial injury due to viral, and bacterial infections, allergens, chemical irritants, and trauma lead to secretion of alarmin cytokines, including IL-25, IL-33, and TSLP. IL-33 plays an important role in activating Th2 lymphocytes, group 2 innate lymphoid cells, dendritic cells, mast cells, basophils, and eosinophils, which result in secretion of cytokines, such as IL-4, IL-13, and IL-5; chemokines, including CCL2, and CXCL8, and adhesion molecules. The inflammatory mediators promote eosinophilic airway inflammation, airway hyperresponsiveness, and remodeling. IL-33 signaling is via a complex heterodimeric receptor comprising of IL-1 receptor-like 1 (IL-1RL1), and IL-1 receptor accessory protein. Downstream signaling cascade leads to the transcription of multiple cytokines and chemokines, which orchestrate eosinophilic asthma. Treatment of severe eosinophilic asthma include long-acting beta2-agonists, and inhaled corticosteroids, and addition of biologics at GINA step 4/5, such as omalizumab, mepolizumab, dupilumab, and tezepelumab. Currently, there are no anti-IL-33 biologics which have been approved for the treatment of eosinophilic asthma. Etokimab is a first-in-class IgG1 monoclonal antibody which blocks the activity of IL-33, thereby, inhibiting its biological effects. Phase 2a proof-of-concept clinical trial in 25 patient with severe eosinophilic asthma, showed that a single intravenous dose of etokimab (330 mg) resulted in a rapid and sustained improvement in lung function, and reduction in the asthma control questionnaire-5 scores throughout the study period of 64 days. Recently, itepekimab has been shown to improve asthma control, lung function, and quality of life, although the effects of itepekimab were slightly lesser than those observed for dupilumab. The dual therapy of itepekimab plus dupilumab did not achieve optimal outcomes, moreover, treatment with the doublet resulted in minimal change in pre-bronchodilator FEV1 compared with placebo. Dual blockade of interleukins incriminated in the pathogenesis of eosinophilic asthma need further careful studies, because of the immunological consequences in the era of SARS-CoV-2.

Keywords: interleukin-33, eosinophilc asthma, biologics, etokimab, itepekimab

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Abbeviations: ACAM-1, intracellular adhesion molecule-1; ACQ-5, five-item asthma control questionnaire; ACQLQ(S), asthma quality of life questionnaire with standardized activities; AHR, airway hyperresponsiveness; AP-1, activator protein-1; ASM, airway smooth muscle; BAL, bronchoalveolar lavage; CXCL, C-X-C motif chemokine ligand; DAMP, damage associated molecular pattern; DCs, dendritic cells; DPP-4, dipeptidyl peptidase-4; ERK, extracellular receptor kinase; FeNO, fractional exhaled nitric oxide; FEV1, forces expired volume in one second; GINA, global initiative for asthma; H2A-H2B, histone-2A-histone 2B; HMGB-1, high-mobility group box protein 1; ICAM-1, intracellular adhesion molecule-1; ICS, inhaled corticosteroids; IgE, immunoglobulin E; IL, Interleukin; ILC2s, group 2 innate lymphoid cells; IL-1RAcP, interleukin-1 receptor accessory protein; IL-1RL1, interleukin-1 receptor-like 1; JAK, janus kinase pathway; LABA, long-acting beta2-agonist; LTRA, leukotriene receptor antagonist; MAPK, mitogen-activated protein kinase; MyD88, myeloid differentiation primary response 88; NF-HEV, nuclear factor-high endothelial venules; NF-kB, nuclear factor kappa-light-chain-enhancer of activated B cells; NKs, natural killer cells; OCS, oral corticosteroids; PI3K, phosphoinositide 3-kinase; Th2, T helper type 2 lymphocyte; SNOT-22, sino-nasal outcome test 22; ST2, suppression of immunogenicity 2; TRAF6, tumour necrosis factor receptor (TNFR)-associated factor 6; Treg, regulatory T cells; TSLP, thymic stromal lymphopoietin; VCAM-1, vascular cell addesion molecule-1

Introduction

Asthma is a significant public health problem, affecting more than 358 million individuals globally,[1] and its prevalence has been increasing in many countries worldwide during the past 40 years.[1-3] It is a common chronic inflammatory airway disease with distinct phenotypes, characterized by different pathophysiological mechanisms, clinical features, disease severity, and response to treatment.[4-9] Severe asthma can be difficult to treat, and still poses an exceptionable health, and pharmaco-economic burden; and consumes a substantial proportion of the health care costs.[9]

Asthma has been classified into several cellular, molecular, and immunogenetic phenotypes.[10,11] which respond differently to treatment, such as corticosteroids, and the new biologics. Clinically, it is classified into four phenotypes established on induced sputum cytology, such as eosinophilic, neutrophilic, mixed granulocytic, and paucigranulocytic asthma.[5-12] Approximately 40-60% of patients with severe asthma have eosinophilic phenotype,[13-17] and eosinophilic asthma is the most common phenotype in children presenting with severe acute asthma.[18]

Eosinophilic asthma

Eosinophilic asthma is the best known phenotype of asthma, characterized by airway and blood eosinophilia, increased synthesis of immunoglobulin E (IgE), and airway hyperresponsiveness (AHR).[19] Comprehensive knowledge has been gained in understanding the pathophysiology, diagnostic biomarkers,[20,21] and novel treatments, including biologics for the treatment of severe eosinophilic asthma.[22-24]

$CD4^+$ T helper lymphocytes (Th2), group 2 innate lymphoid cells (ILC2s), dendritic cells (DCs), mast cells, basophils, and eosinophils play a key role in the pathogenesis of Th2-driven eosinophilic asthma. Eosinophilic asthma is preferably termed type 2-high, because several cell types secrete the inflammatory cytokines perpetuating eosinophilic airway inflammation.[25] Clinically, eosinophilic asthma is characterized by moderate-to-severe disease, frequent exacerbations, hospitalization; and poor lung function, and worse health-related quality of life (HLQoL).[26,27]

During allergic inflammation, both Th2 lymphocytes, ILCs secrete multiple cytokines, such as IL-4, IL-13, and IL-13, chemokines, including CCL2, CCL5, CXCL8, and CXCL10, adhesion molecules, and growth factors.[19,28-31] which promote airway inflammation, airway hyperresponsiveness, and remodeling. Table 1 shows the inflammatory mediators, including growth factors implicated in the pathogenesis of severe eosinophilic asthma.

Epithelial cells play a sentinel role in the regulation of tissue homeostasis by producing and secreting numerous proteins, such as antioxidants, cytokines, chemokines, growth factors, and lipid mediators.[32,33] Damaged or dysfunctional epithelium produce large quantities of cytokines, and growth factors which interact with the underlying mesenchymal cells, including fibroblasts and myofiblobasts, resulting in epithelial-mesenchymal transition (EMT), and airway remodeling.[34,35]

Epithelial cells insult due to allergens, pollutants, viral and bacterial respiratory infections, and trauma release three "alarmin" cytokines, including IL-25, IL-33, and thymic stromal lymphopoietin (TSLP).[32,33] The triplet, although they belong to different cytokine families, play synergistic roles in the pathophysiology of severe eosinophilic asthma. Epithelial-derived cytokines are favorable targets for the development of new biologics for the treatment, and prophylaxis of asthma, particularly due to asthma exacerbations triggered by respiratory viral infections.

The new kid in the IL-1 family, IL-33 plays a central role in the pathogenesis of eosinophilic asthma, and is of clinical importance because it is implicated in the pathogenesis of other allergic diseases, such as food allergy,[36] allergic rhinitis,[37,38] chronic rhinosinusitis with nasal polyps CRSwNP),[39,40] allergic conjunctivitis,[41] and atopic dermatitis.[42,43]

Interleukin-33 and alarmin cytokines

Interleukin-33 belongs to the IL-1 family of cytokines, which has 11 members, including IL-1α, IL-1β, IL-1Ra, IL-18, IL-36α, IL-36β, IL-37, IL-38., etc, and signals via 10 receptors, coreceptors, decoy receptors, and inhibitory receptors.[44,45] Interleukin-33 mediates Th2 immune responses, and promotes eosinophilic inflammation, unlike the other members which promote Th1 inflammatory responses.[46,47] Its immunopathological effects are similar to those of the other epithelial-derived cytokines, such as IL-25, and TSLP in driving Th2-mediated eosinophilic airway inflammation.

Epithelial injury due to viral, and bacterial infections, allergens, chemical irritants, and trauma lead to secretion of alarmin cytokines, including IL-25, IL-33, and TSLP.[48,49] Alarmin cytokines play an instigating and central role in the pathogenesis of Th2-driven allergic diseases.[50] They can activate Th2 lymphocytes, dendritic cells, regulatory cells (Treg),[51,52] group 2 innate lymphoid (ILC2) cells,[53] nuocytes,[54] mast cells,[55] basophils and eosinophils[27] to secrete several cytokines, chemokines, adhesion molecules, and growth factors, which lead to eosinophilic airway inflammation, airway hyperresponsiveness (AHR), and remodeling.

Interleukin-33

Interleukin-33, also termed IL-1F11 or NF-HEV is a newly described and celebrated member of the IL1 family.[44,56] It was first identified through a database search of human genome using compilation of the other IL-1 family members.[57] IL-33 is principally produced by epithelial cells following insults from allergens, viral, bacterial, and fungal infections, chemical irritants, and trauma.[48,49] Interleukin-33 is also secreted and expressed by several immune cells, such as Th2 lymphocytes, ILC2 cells, dendritic cells, Treg cells, mast cells, macrophages, basophils, and eosinophils; and non-immune cells, including fibroblasts, airway smooth muscle (ASM) cells, and endothelial cells.[56,58]

Interleukin-33 is localized to the nucleus due to its association with heterochromatin, and mitotic chromatin, via a conserved homodomain-like-helix-turn-helix motif within its N-terminal part.[59,60] In the nucleus it acts as a transcription factor,[61,62] similar to IL-1α, and high-mobility group box protein-1 (HMGB-1); although its actual role as a nuclear factor is not fully understood.[59] Thus, like IL-1α, and HMGB-1, IL-33 is considers as a damage associated molecular pattern (DAMP) molecule, that is released after tissue injury or trauma.[58] IL-33 is usually released by necrotic or apoptotic cells without cleavage by caspace-1 and calpain.[63,64]

Interleukin-33 (IL-33FL) consists of 270 amino acids, and has a molecular mass of 30 kDa.[57] Unlike IL-1 and IL-18, the full-length is bioactive even without caspase-dependent cleavage.[63,65] It can be split at a conservative cleavage site at Asp D178 by caspase-1, -3, and caspase-7. Cleavage reduces its half-life.[66] However, the cleaved form of IL-33 produced by proteolytic actions of neutrophil elastase and cathepsin G has 10-fold higher biologic activity than the full-length form.[67]

Interleukin-33 signaling

The interleukin-33 receptor (IL-33R), is also termed as ST2, DER4, or Fit-1 is a heterodimer belonging to the Toll/IL-receptor family. IL-33 signaling is via a complex heterodimeric receptor comprising of IL-1 receptor-like 1 (IL-1RL1, popularly known as ST2), and IL-1 receptor accessory protein (IL-1RAcP).[68-70] Transduction of IL-33R signalling is by inducing activation of transcription factors, such as NF-kB, and AP-1 via a signaling pathway consisting of recruitment of myeloid differentiation factor 88 (MyD88), TNF receptor associate factor (TRAF6), and/or mitogenic-activated protein kinase (MAPK) after binding to IL-33.[71] Finally, NF-kB and AP-1 bind to DNA and induce the expression of various cytokines, chemokines, and adhesion molecules from the effector cells. Interleukin-33 also induces the phosphorylation and activation of extracellular signal-regulated kinase (ERK1/2), c-Jun N-terminal kinase (JNK1/2)-activator protein-1 (AP-1), p38, JAK2, and PI3K/AKT signaling pathways.[72] This results in the production, and release of cytokines, chemokines, and growth factors by multiple immune, and inflammatory cells. The inflammatory mediators, and growth factors lead to eosinophilic inflammation, AHR, airway remodeling, and severe eosinophilic asthma.

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Table 1 Inflammatory mediators, and growth factors implicated in the pathogenesis of severe eosinophilic asthma

Th2 cytokines	**Chemokines**
IL-5	CCL2 (MCP-1, 3, 5)
IL-4	CCL5 (RANTES)
IL-13	CCL11 (eotaxin)
Epithelial-derived cytokines	
IL-25	CXCL8 (IL-8)
IL-33	CX3CL1 (Franktalkine)
TSLP	
Lipid mediators	**Growth factors**
Leukotriene D4 (LTD4)	TGF-β1
Prostaglandin E2 (PGE2)	bFGF-1
Thromboxane A2 (TXA2)	PDGF-BB
Platelet activating factor (PAF)	IGF-2, IGF-2
Adhesion molecules	VEGF-1
ICAM-1	Angiogenin, Angiopoietin
VACM-1	

Abbreviations: IL, interleukin; TSLP, thymic stromal lymphopoietin; CXCL: C-X-C motif chemokine ligand; MCP-1, monocyte chemotactic protein-1; RANTES: regulated on activation, normal T-cell expressed and secreted; TGF-β, transforming growth factor-β; FGF, fibroblast growth factor; PDGF, platelet-derived growth factor; IGF, insulin-like growth factor; VEGF, vascular endothelial growth factor; ICAM-1, intracellular adhesion molecule-1; VCAM-1, vascular cell adhesion molecule-1.

Table 2 Dosages of approved biologics by the food and drug administration for the treatment of severe eosinophilic asthma

Biologic	**Dosage**	**Efficacy**
Omalizumab*	75-375 mg SC Q 2/4 wk	Reduces exacerbations (47-53%)
Mepolizumab*	100 mg SC Q 4 wk	Reduces exacerbations (50-60%)
Reslizumab	3 mg/kg IV Q 4 wk	Reduces exacerbations (34-75%)%
Benralizumab*	30 mg SC Q 8 wk	Reduces exacerbations (25-60%)
Dupilumab*	200 mg or 300 mg SC Q 2 wk	Reduces exacerbations (60-80%)
Tezepelumab	210 mg SC Q 4 wk	Reduces exacerbations (41-56%)

Abbreviations: IV, intravenous, given over 25-50 min; SC, subcutaneous, Q, every; wk, weeks. *Approved for the treat of childhood eosinophilic asthma. Pediatric dosages depend on age, and body weight of the child or adolescent.

Table 3 Adverse events of itepekimab and dupilumab in patients with moderate-to severe asthma

Adverse event	**Placebo Itepekimab**	**Itepekimab plus Dupilumab**
Nasopharyngitis 12%	18%	11%
Allergic rhinitis 1%	4%	0%
Nausea 3%	5%	3%
Backache 1%	5%	3%

Interleukin-33 immunopathological roles in eosinophilic asthma

Interleukin-33 plays an initiating and key role in promoting Th2 allergic responses and eosinophilic asthma. Unregulated activity of IL-33 result in activation of Th2 lymphocytes,[47,57] NKT and NK cells,[73] ILCs,[74,75] dendritic cells,[76] mast cells,[77] basophils,[78] and eosinophils.[46,78] Furthermore, IL-33 can activate non-immune cells, and structural cells, such as epithelial cells,[79] fibroblasts, ASM cells, and macrophages,[57] leading to the production of more cytokines, chemokines, and growth factors, embellishing the inflammatory, and remodeling process.

During allergic inflammation, all of the aforementioned cells are capable of secreting cytokines, such as IL4, IL-13, and IL-5;[57] chemokines, including CCL2, CCL5, and CXCL1, CXCL8, CXCL10;[3] and adhesion molecules, such as ICAM-1, and VCAM-1.[46,80] These mediators orchestrate eosinophilic inflammation, goblet cell hyperplasia and mucus hypersecretion, AHR, and airway remodeling, leading to airflow obstruction, and severe eosinophilic asthma.

Human eosinophils express (IL-1R1L1),[46,79] and IL-33 has been reported to promote eosinophil adhesion via expression of adhesion molecules, such as ICAM-1, and VACM-1, and eosinophil survival by foiling apoptosis.[46,80] Furthermore, IL-33 potentially activates eosinophils to secrete cytokines, such as IL-6, and IL-9; chemokines including CCL2, and CXCL8 (IL-8); eosinophilic cationic proteins (ECP), and superoxides.[46,78,79] Eosinophilic cation proteins are very toxic, and damaging to the airway epithelium.

Interleukin-33 plays an important role in inducing AHR, and persistent asthma.[74,75] The crosstalk between epithelial cells and ILC2s plays an important role in maintaining chronic severe asthma. Epithelial cell-derived IL-33 induces ILC2s to secrete IL-13, which upregulates IL-33 receptors to release more IL-33, thus establishing a feed-forward circuit.[75] IL-33 acting in collaboration with IL-13, and IL-4, promote airway inflammation,[81] goblet cells hyperplasia and mucus hypersecretion,[82] enhanced ASM activity,[83] and airway remodeling.[83] Additionally, increased expression of IL-33 is associated with increased reticular basement thickening in endobronchial specimens from children with severe corticosteroid-resistant asthma.[84] Severe asthma is characterized by angiogenesis, and lymphangiogenesis,

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and expansion of tortuous dilated blood vessels, and mucosal edema, which contributes to airflow obstruction. Murine models of asthma have shown that IL-33 induces expression of multiple angiogenic factors, and promotes angiogenesis.[85] Furthermore, IL-33 may be associated with corticosteroid insensitivity in children with severe asthma.[40,86]

Genomic studies have identified the susceptibility polymorphisms in IL-33, and IL-1 receptor-like 1 (IL-1RL1) associated with persistent wheezing and asthma in children, such as r4742170, rs7037276, and rs1342326.[87] Schröder et al.[88] have reported that polymorphisms, including rs928413, and rs1342326 are associated with asthma and allergic rhinitis. These studies indicate that IL-33 may play an important role in the development of asthma, and allergic rhinitis.

Several studies have reported increased expression of IL-33 and its receptor ST2 in bronchial biopsies, bronchoalveolar lavage (BAL) fluid, sputum, and serum from patients with asthma compared to healthy controls. Increased expression of IL-33 in epithelial cells,[89] ASM cells,[83] BAL fluid, and sputum,[90] has been reported in patients with asthma, and correlate with disease severity.[83,90] Similarly, serum levels of IL-33 and its receptor ST2 have been shown to be elevated in children,[91] and adults[92] with asthma, and the levels correlate with the severity of the disease.[91,92]

Treatment of eosinophilic asthma

The majority of patients with stable asthma, including eosinophilic phenotype respond to stepwise treatment with standard therapies, such as long-acting β2-agonists (LABA), low dose inhaled corticosteriods (ICS), and leukotriene receptor antagonists (LTRA), such as such as the Global Initiative for Asthma (GINA) guidelines,[93] and British Thoracic Society, Scottish Intercollegiate guidelines.[94] However, about 15-20% of patients have difficult to control asthma, and remain symptomatic, with frequent exacerbations, increased use of ICS or OCS, recurrent emergency room admissions, and impaired quality of life.[95] Approximately, 3.6-10% asthmatics have severe refractory corticosteroid-resistant disease, which is inadequately controlled despite treatment with LABA, high dose ICS or OCS, and/or LTRA.[96,97] Approximately, 50% of these patients have Th2-mediated severe eosinophilic asthma.[97]

Biologics for the treatment of severe eosinophilic asthma

Th2 cytokines, such as IL-4, IL-13. IL-5, IL-25, IL-33, and TSLP play a key role in the pathogenesis of eosinophilic asthma. Several biologics which target immunoglobulin E (IgE), and interleukins are currently approved by the U.S. Food and Drug Administration (FDA), and the European Medicines Agent (EMA) for personalized treatment of asthma. They include omalizumab (anti-IgE),[98,99] mepolizumab (anti-IL-5),[100-102] reslizumab (anti-IL-5),[103,104] benralizumab (anti-IL-5R),[105-107] dupilumab (anti-IL-4Rα),[108,109] and tezepelumab (anti-TSLP),[110,111] for add-on treatment of severe eosinophilic asthma. Mepolizumab and benralizumab are also approved for treatment of severe eosinophilic asthma in children aged 6 years and above, and dupilumab is approved for treatment of severe eosinophilic asthma in children of 12 years and older. Table 2 shows the approved biologics and their dosages for the treatment of adults with severe eosinophilic asthma.

Biologics have been shown to be very effective in reducing asthma symptoms, annualized exacerbation rates, hospitalization, emergence room visits; and improve lung function, and health-related quality of life (HLQoL). Additionally, they allow patients to wean or discontinue corticosteroid treatment,[101,106,108] thus minimizing the serious adverse events associated with glucocorticoid therapy.

The GINA guidelines,[93] and British Thoracic Society, Scottish Intercollegiate guidelines recommend initiation of anti-IgE at step 5.[94] The National Asthma Education and Prevention Program, Expert Panel Report 3 (ERP 3) guidelines also recommend eosinophilic asthma IgE targeted biologics, and interleukin monoclonal antibody therapy at step 5.[112]

However, biologics are only effective in patients with Th2-driven eosinophilic asthma,[113-115] and a subgroup of patients with eosinophilic are inadequately controlled on some of the biologics. Furthermore, although biologics may improve symptoms, exacerbation rates, and lung function, they have not been shown to modify the disease process, or provide lasting benefits after discontinuation.[116] Additionally, they only reduce the annualized exacerbation rates by 25% (omalizumab[117]) up to 60% (dupilumab[118]), depending on the authors, and most important, the levels of the biomarkers of eosinophilic inflammation. Patients with high eosinophil count ≥ 150 cells/μL, serum IgE, FeNO ≥ 25 parts per billion (ppb), perisotin, and dipeptidyl peptidase-4, respond favourably to biologics compared to those with low values.

In clinical practice, patients should be phenotyped with biomarkers of eosinophilic inflammation, such as eosinophil count, serum IgE, fractional exhaled nitric oxide (FeNO), periostin, dipetidyl peptidase-4 (DPP-4), and osteopontin before initiation of targeted biologics.[117-122] Patient selection using biomarker of eosinophic inflammation, and consideration of comorbidities with eosinophilc asthma, such as allergic rhinitis, atopic dermatitis, and chronic rhinosinusitis with nasal polyps is very important in considering initiation of the expensive biologics.[123] Some biologics, such as dupilumab are effective in the treatment of all aforementioned co-existing diseases with eosinophilic asthma, and may be beneficial, and advantageous in patient with asthma and comorbidities.[124]

Anti-interleukin-33 biologics

Currently, there are no anti-IL-33 biologics approved by the Food and Drug Administration, and the European Medicines Agency, although there a few IL-33 antagonists in different stages of development.

Etokimab

Etokimab (AnaptysBio, Inc.) is a first-in-class IgG1 monoclonal antibody which blocks the activity of IL-33, thereby, inhibiting its biological effects. Phase 2a proof-of-concept clinical trial in 25 patient with severe eosinophilic asthma, showed that a single intravenous dose of etokimab (330 mg) resulted in a rapid and sustained improvement in lung function (FEV1), and reduction in the asthma control questionnaire-5 (ACQ-5) scores, throughout the study up to day 64, compared with placebo. The ACQ-5 scores decreased in the etokimab group by 0.52 over placebo at day 8, and were sustained to 0.54 over placebo at day 64. At day 64, etokimab demonstrated an 11% increase in FEV1 over placebo. Etokimab was well tolerated with no adverse events were reported.[125] However, the number of patients studied in this clinical trial was small.

AnaptysBio Inc., has discontinued clinical trials on etokimab for the treatment of eosinophilic asthma. This follows the disappointing phase II results of etokimab for the treatment of chronic rhinosinusitis with nasal polyps. Etokimab did not achieve statistically significant improvement in bilateral nasal polyp score, and the Sino-Nasal Outcome Test score (SNOT-22) score over placebo.[126]

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Itepekimab

Itepekimab is a new human IgG4P monoclonal antibody against the upstream alarmin cytokine IL-13. Recently, phase II randomized, double-blind, placebo-controlled trial investigated the efficacy and safety of subcutaneous itepekimab 300 mg (Sanofi/Regeneron) in 296 adults with moderate-to-severe asthma on inhaled corticosteroids, and long-acting beta2-agonists.[126] At 14 weeks, there were significantly less patients who had lost asthma control in the itepekimab group compared with placebo (22% versus 41%; P < .02). Similarly, there were significantly less patients who had lost asthma control in the dupilumab group compared with placebo (19% versus 41%). However, there was no significant difference in asthma control in the itepekimab plus dupilumab compared with the placebo group (27% versus 41%; P = .07).

The pre-bronchodilator FEV1 increased among patients in the itepekimab-alone group compared to placebo group (mean difference 0.14 liters; 95% confidence interval (CI), 0.01-0.27), and in the dupilumab-alone group compared with placebo (mean difference 0.16 liters; 95% CI, 0.03-0.29). Again, there was no much difference in the pre-bronchodilator FEV1 in the itepekimab plus dupilumab group compared with the placebo group (mean difference 0.1 liters; 95% CI, -0.03-0.23).[126]

Single subcutaneous injection of itepekimab resulted in improvement in the five-item Asthma Control Questionnaire (ACQ-5), Asthma Quality of life Questionnaire with Standardized Activities (AQLQ(S), and lung function (FEV1)). Itepekimab also significantly and drastically reduced the mean blood eosinophil count.

Although this study was not specifically intended as head-to head comparison of dupilumab "the super gunner" versus itepekimab, the effects of dupilumab were generally greater than those observed with itepekimab, particularly in patients with type 2 asthma. Dupilumab might have been more effective because it blocks more type 2 immunopathological pathways (IL-4/IL-13 axis). Nevertheless, the new kid biologic in the treatment of eosinophilic asthma, itepekimab is effective, safe and well tolerated by patients. It is not clear why two biologics targeting two different interleukin pathways (IL-4/13 and IL-33) did not achieve synergistic effects in improving asthma control, lung function, and quality of life.[126]

Adverse events were numerically higher in patients treated with itepekimab compared to patients treated with dual biologics, or placebo (70% versus 66%).[126] Table 3 shows the adverse effect of itepekimab and dupilumab in patients with moderate-to-severe asthma. Dual biologic treatment is feasible in the treatment of cancer, and even asthma. However, there are concerns regarding immunosuppression in the era of SARS-CoV-2, particularly combinations of approved biologics with established side effects, plus biologics still in clinical trials.

Conclusion

Eosinophilic asthma is characterized by moderate-to-severe disease, frequent exacerbations, hospitalization; and poor lung function, and worse health-related quality of life. Th2 lymphocytes, and ILCs cytokines, such as IL-4, IL-13, and IL-5; and epithelial-derived cytokines, including IL-25, IL-33, and TSLP play a key role in the pathogenesis of eosinophilic asthma. Eosinophilic asthma is one of the phenotypes of asthma which is responsive to biologics, such as omalizumab, mepolizumab, dupilumab, and tezepelumab. However, biologics do not completely prevent exacerbations in a subgroup of patients with eosinophilic asthma. Furthermore, they have not been shown to modify the disease process, or provide lasting benefits after discontinuation. There is unmet need to develop novel biologics, particularly targeting the sentinel cytokines, such as IL-33. Itepekimab is a monoclonal antibody targeting IL-33. Single subcutaneous injection of itepekimab has been shown to reduce exacerbations, and improve asthma control, lung function, and HLQoL. The effects of itepekimab was almost similar to those achieved by dupilumab, athough the outcomes were slightly less. However, dupilumab plus itepekimab treatment did not achieve the expected benefits. Dual biologic for the treatment of eosinophilic requires further investigations, because of the risk of immunosuppression in the era of SARS-CoV-2.

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None.

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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