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# Immunologic Basis of Type 2 Biologics for Severe Asthma

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**Conflict of Interest**
The authors declare no potential conflicts of interest.

**Abbreviations**
AEC, airway epithelial cell; AERD, aspirin-exacerbated respiratory disease; AHR, airway hyperresponsiveness; CysLT, cysteinyl

## ABSTRACT

Asthma is a chronic airway inflammatory disease characterized by reversible airway obstruction and airway hyperreactivity to various environmental stimuli, leading to recurrent cough, dyspnea, and wheezing episodes. Regarding inflammatory mechanisms, type 2/eosinophilic inflammation along with activated mast cells is the major one; however, diverse mechanisms, including structural cells-derived and non-type 2/neutrophilic inflammations are involved, presenting heterogenous phenotypes. Although most asthmatic patients could be properly controlled by the guided treatment, patients with severe asthma (SA; classified as a treatment-refractory group) suffer from uncontrolled symptoms with frequent asthma exacerbations even on regular anti-inflammatory medications, raising needs for additional controllers, including biologics that target specific molecules found in asthmatic airway, and achieving the precision medicine for asthma. This review summarizes the immunologic basis of airway inflammatory mechanisms and current biologics for SA in order to address unmet needs for future targets.

**Keywords:** Asthma; Biologics; Inflammation; Phenotype; Precision medicine; Eosinophils

## INTRODUCTION

Asthma is the most common chronic inflammatory disease of the airways driven by interactions between genetic/epigenetic factors and environmental exposure (1). It is recognized as a major global health problem because asthma prevalence and mortality have been progressively increasing during recent decades, placing a significant burden on patients and society (2). Even more, some asthmatic patients (called those with severe asthma, SA) remain uncontrolled despite regular treatment including medium-to-high-dose inhaled corticosteroid (ICS) plus long-acting beta 2 agonist with proper inhaler technique and adherence. They suffer from persistent symptoms, and have higher risks of comorbidities and asthma exacerbations, impacting on poor quality of life (3,4). Therefore, more efforts are needed for the correct diagnosis of SA, active patient education with self-management strategies, and developing additional targets, which will address major unmet needs in SA (5). Recently, several type 2 biologics have been approved for their safety, efficacy, mechanism of action, and indications (6). The emergence of these novel agents has provided targeted therapies for SA, but therapeutic options are not enough. Here, we explore potential future targets for SA by understanding its immunological mechanisms.

leukotriene; ECP, eosinophil cationic protein; EDN, eosinophil-derived neurotoxin; EET, eosinophil extracellular trap; FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroids; ILC, innate lymphoid cell; NA, neutrophilic asthma; NET, neutrophil extracellular trap; OCS, oral corticosteroids; RANTES, regulated on activation, normal T cell expressed and secreted; SA, severe asthma; ST2, suppression of tumorigenicity 2.

**Author Contributions**

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## ASTHMA PHENOTYPES

### Definition of SA

The phenotype of SA includes difficult-to-treat or poorly controlled asthma. Although the majority of adult asthmatic patients have achieved disease control with the standard therapy including maintenance treatment of ICS with/without long-acting beta 2 agonist, 5%–10% of them (classified as SA) remain in uncontrolled status and suffer from frequent asthma exacerbations (7). Understanding immunologic mechanisms (with complexity) in the pathogenesis of SA has led to the development of new therapeutic targets for better management. Typically, SA has been classified into type 2 and non-type 2 asthma according to inflammatory cell phenotypes (increased eosinophil vs. neutrophil counts in blood/sputum), regardless of atopic status. Many researchers and clinicians have recognized asthma as a heterogenous disease with multiple phenotypes (8), but preferentially distinguishing type 2 from non-type 2 asthma when considering biologic therapies.

### Type 2 asthma

More than 50% of patients with SA present type 2 inflammation with common characteristics, such as activation of mast cells and eosinophils (9), resulting in airway hyperresponsiveness (AHR) and reversible airway obstruction followed by airway remodeling (10,11). Blood and sputum eosinophilia as well as high levels of serum IgE, eosinophil-derived neurotoxin (EDN), and fractional exhaled nitric oxide (FeNO) are key findings for representing the phenotype of type 2 asthma (12-14). Moreover, emerging evidence has revealed that eosinophil extracellular traps (EETs) containing cytotoxic granule proteins and mediators are involved in the pathogenesis of SA (15-17). In addition to mediators related to immune cells, epithelium-derived cytokines, including IL-25, IL-33, and TSLP, which subsequently induce activation of group 2 innate lymphoid cells (ILC2s), have been emphasized in SA with persistent eosinophilic airway inflammation (18). Furthermore, close interplays between airway epithelial cells (AECs) and immune cells (increased levels of folliculin and dipeptidyl peptidase 10, but decreased levels of surfactant protein D) could induce airway inflammation, and remodeling has been demonstrated in patients with aspirin-exacerbated respiratory disease (AERD), a phenotype of SA (19-25). Although many molecules have been highlighted in type 2 asthma related to disease severity, recent biologics under clinical trials mainly focus on targeting IL-4, IL-5, IL-33, and TSLP. Therefore, future therapeutic targets remain to be developed, considering complicated immune responses in SA.

### Non-type 2 asthma

The pathophysiological mechanism of non-type 2 asthma, including neutrophilic and pauci-granulocytic asthma, remains poorly understood compared to type 2 asthma. Nevertheless, many studies have suggested that non-type 2 asthma is associated with Th1/Th17 cell activation, showing higher levels of IL-17 in SA (26,27). In addition, a recent paper demonstrated the contribution of G-CSF in neutrophilic inflammation of the asthmatic airways (28). Furthermore, extracellular traps released by activated neutrophils (defined as neutrophil extracellular traps, NETs) have been involved in non-type 2 asthma via stimulating airway epithelium (29,30). Especially, S100 calcium-binding protein A9 and amyloid A1 have been shown to enhance the production of NETs as well as neutrophil activation in adult asthmatic patients with severe neutrophilic inflammation, in which activated M1 macrophages are involved (31,32), suggesting close interactions between neutrophils/macrophages and AECs in patients with neutrophilic inflammation found in SA. In addition, patients with SA are older and less sensitive to current anti-inflammatory treatment

(especially, corticosteroids). However, these patients still rely on conventional therapies because currently approved biologics for treatment of non-type 2 asthma are still lacking, which is an urgent unmet need for SA.

## ASTHMA AND IMMUNE CELLS

### Mast cells and basophils

Asthma is associated with both innate and adaptive immunity mediated by various immune cells as summarized in **Fig. 1**. Among them, mast cells and basophils share many features as key granulocytes for IgE-dependent inflammation by expressing high affinity receptor for IgE. However, some different functions in immunological and biochemical mechanisms between these 2 cells have been suggested in asthma. Mast cells are tissue-resident cells and localized in airway smooth muscle, while basophils circulate in blood and infiltrate inflamed sites (33). Nevertheless, both cells are recruited to the lungs by chemotactic activity of regulated on activation, normal T cell expressed and secreted (RANTES) and eotaxin-1/2 released from AECs. They interact with AECs and other immune cells, releasing various molecules, including histamine, cytokines, and chemokines, via IgE-mediated activation or degranulation (34). Among them, histamine causes acute-phase reactions in asthma as a strong inducer of airway smooth muscle constriction and mucus secretion (35). Similarly, cysteinyl leukotrienes (CysLTs, including leukotriene C4/D4/E4) and prostaglandin D2 are major products from mast cells and basophils, which act as potent bronchoconstrictors. Furthermore, both cells produce IL-4 and IL-13 responsible for Th2 cell differentiation and B cell class switching (36). Especially, IL-33 and TSLP (known as alarmins), derived from AECs in response to viral infection, pollutants or allergens, induce activation and degranulation of these cells, highlighting the importance of their interaction with AECs in SA as well as in allergic asthma (37,38).

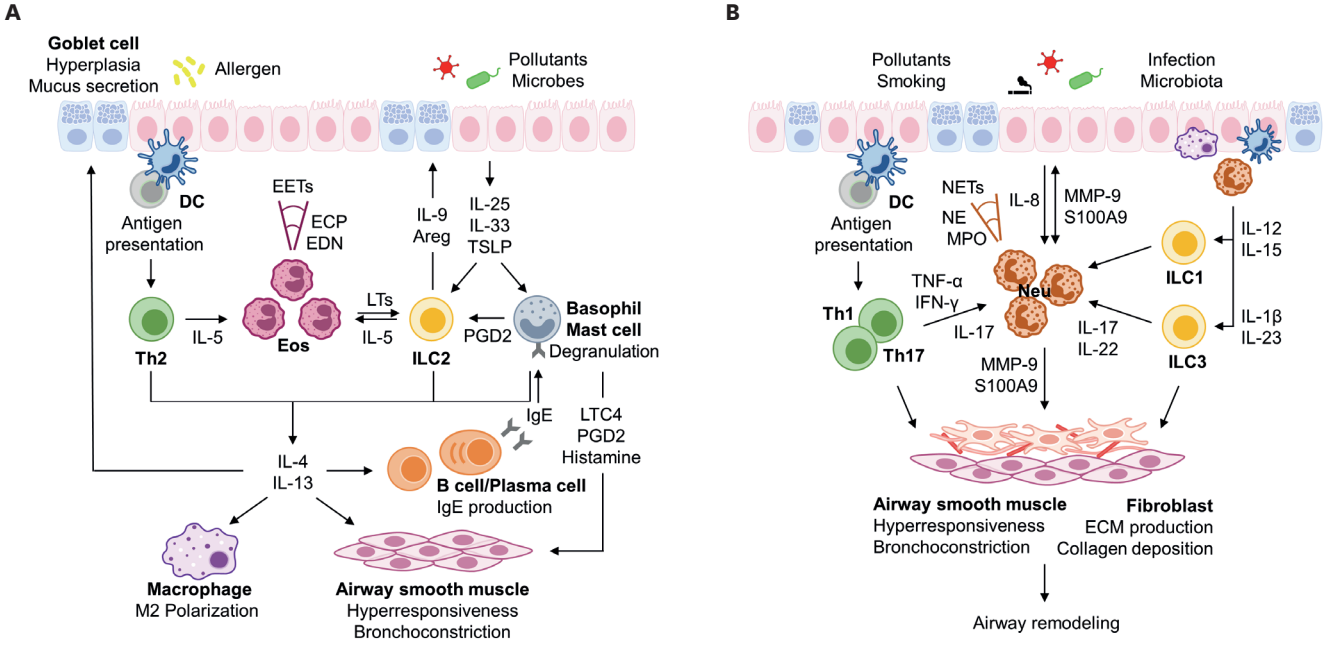


**Figure 1.** Pathological mechanism of Innate and adaptive immune response in type 2 (A) and non-type 2 asthma (B).
DC, dendritic cell; Eos, eosinophil; Areg, amphiregulin; LT; leukotriene; PGD2, prostaglandin 2; LTC4, leukotriene C4; Neu, neutrophil; NE, neutrophil elastase; MPO, myeloperoxidase; MMP-9, matrix metalloprotease-9; S100A9, S100 calcium-binding protein A9; ECM, extracellular matrix.


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## Eosinophils

Eosinophils are major effector cells driving type 2 immune response and allergic inflammation in asthma pathogenesis. Therefore, increased blood eosinophil count is a useful indicator for the determination of asthma phenotype and disease severity (39). Eosinophils regulate inflammatory status by releasing various cytokines, such as G-CSF, IL-1α, IL-2, IL-3, IL-4, IL-5, IL-6, IL-9, IL-10, IL-13, IL-16, IL-17, IL-25, TNF-α, and TGF as well as chemokines such as IL-8, MIP-1α, RANTES, and eotaxins (40). In particular, IL-5 plays an important role in the survival and degranulation of eosinophils in an autocrine manner, affecting asthma severity and the frequency of asthma exacerbation (41). Moreover, eosinophils have abundant proteins within granules, including EDN, eosinophil cationic protein (ECP), and eosinophil peroxidase, and major basic protein, which are released when eosinophils are activated (42). Recently, serum EDN has been considered a potential biomarker for the phenotype of SA by mirroring eosinophil activity and EETs-forming eosinophil counts (43). Although these granules predominantly localized in EETs have been suggested to combat against helminth or bacteria during infection, excessive release of EETs drives persistent eosinophilic inflammation and tissue damage in the airways by the activation of innate immune responses orchestrating an interaction between AEC and ILC2s, as well as Th2 responses, which enhances persistent eosinophilic inflammation and lung function impairments as key features of SA (15,16). Eosinophils also secrete various lipid mediators, such as leukotrienes and prostaglandins, through 5-lipoxygenase and cyclooxygenase pathways. Dysregulated arachidonic acid metabolism with CysLTs overproduction and prostaglandin E2 reduction is a main feature of AERD, which is a phenotype of severe type 2/eosinophilic asthma. Especially, an increased level of urinary leukotriene E4 (which is a stable and final product of CysLTs) is considered a useful biomarker for the diagnosis of AERD (44). In addition, this mediator could induce mast cell and ILC2 activation as well as eosinophils recruitment into the upper and lower airway mucosa, enhancing persistent type2/eosinophilic inflammation in the upper and lower airways of patients with AERD and resulting in poor clinical outcomes of AERD (45,46).

## Neutrophils

Neutrophils act as a first barrier for host defense in innate immunity through phagocytic activity against invading microbes (47). However, massive neutrophil infiltration in the airways as well as higher blood neutrophil counts contributes to uncontrolled symptoms and steroid resistance in asthma. Neutrophilic asthma (NA) is one of the SA phenotypes in responses to environmental pollutants, infection, smoking, and obesity. Increased blood/sputum neutrophil counts is related to asthma severity, in which elevated levels of IL-8 and IL-17 activate and recruit neutrophils into asthmatic airways (11,48) Moreover, neutrophils affect airway microbiota, which is characterized by low diversity, but high pathogenic burdens in bacterial composition (49). Neutrophils produce various cytokines and mediators, which induce fibrotic tissue remodeling in the airways. Upon allergen exposure, matrix metalloprotease-9 with tissue inhibitor of matrix metalloproteinases-1 is generated, enhancing airway inflammation and remodeling in allergic asthma (50,51). Furthermore, activated neutrophils release NETs for antimicrobial defense with a web-like complexity of DNA, histones, and granule proteins such as neutrophil elastase, myeloperoxidase, and cathepsin G (52). However, high prevalence of NETs in the airway results in host damages and activates AECs and eosinophils, driving lung function decline and irreversible airflow obstruction in patients with SA (53,54). Although the role of neutrophils in type 2 asthma is less discussed, the cell has considerable responsibility for persistent symptoms in uncontrolled status and poor response to currently available anti-inflammatory medications in patients with SA, which are the major unmet needs for the management of SA.


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### Macrophages

Macrophages are the richest in the lungs and play critical roles in innate immunity to recognize and clear invading pathogens by phagocytosis. Macrophages have both pro- and anti-inflammatory effects according to their distinct signaling pathway and gene expression (55). Macrophage polarization is critical for determining asthma phenotypes and regulated by complex interactions with various cytokines and mediators. In response to environmental stimuli, macrophages are polarized into M1 type by lipopolysaccharides, TNF-α, and IFN-γ. On the contrary, M2 polarization is predominantly induced by Th2 cytokines (IL-4 and IL-13) during allergic inflammation (56). Especially, arginase-1 is a significant M2 marker in murine allergic asthma as a regulator of endogenous nitric oxide production, though it is not present in human M2 macrophages (57). Moreover, our recent study suggested the role of M1 macrophages to activate neutrophils in patients with NA (31). However, further investigations are needed to elucidate the role of macrophages interplaying with eosinophils and neutrophils, which will be a new target for SA.

### T cells

T and B cells participate in adaptive immunity by antigen-specific responses in asthma. T cells recognize antigens processed by antigen presenting cells, such as macrophages and dendritic cells, and differentiate to their subsets. Among them, the contribution of $CD4^+$ T cells, especially Th1, Th2, and Th17 cells, is well-defined according to asthma phenotypes. Especially, an imbalance between Th1 and Th2 cells has been emphasized in the pathogenesis of type 2 asthma. Th2 cells initiate allergic inflammation and amplify immune responses by interacting with multiple immune cells via cytokines including IL-4, IL-5, and IL-13 (58). Th1 and Th17 cells are closely related to disease severity by driving neutrophilic inflammation and steroid resistance in SA. However, they are also increased in type 2 asthmatic airways during asthma exacerbation in order to suppress an excessive activation of Th2 cells (59,60). By contrast, regulatory T cells suppress allergic inflammation by affecting various immune cells, such as eosinophils, neutrophils, T cells, B cells, ILC2s, mast cells, and macrophages, via their anti-inflammatory mediators (IL-10, TGF-β1, and granzymes) or specific surface molecules (CTLA-4 and OX40). In asthmatic patients, impaired functions of regulatory T cells followed by increased population is commonly observed (61). As T cells play a regulating role in SA, potential biologics controlling their functions are considered future therapeutic targets.

### ILCs

Accumulating evidence has emphasized the importance of ILCs in host defense and mucosal immunity. Without antigen specificity, ILCs rapidly release diverse cytokines in response to innate stimuli. According to their heterogenetic features, ILCs are divided into 3 subtypes. Among them, the role of ILC2s are critical in the development of allergic asthma (62). ILC2s orchestrate dynamic interactions with airway epithelium and immune cells via various cytokines. Especially, IL-25, IL-33, and TSLP, which are derived from AECs by environmental factors, are main stimulators for ILC2s to produce IL-4, IL-5, IL-9, IL-13, and amphiregulin. These mediators enhance Th2 immune response by inducing Th2 cell differentiation, basophil and mast cell activation, and eosinophil recruitment as well as asthma symptoms by increasing mucus production and AHR (63). Especially, ILC2s contribute to steroid resistance of SA in a TSLP-dependent manner, suggesting the need of anti-TSLP Ab as a therapeutic option in SA (64). Although the roles of ILC1s and ILC3s are not fully understood in SA, they have been highlighted in the airway inflammation of non-type 2 asthma (65). Furthermore, recent studies have found that ILC1s and ILC3s affect M1 macrophage polarization in NA, while ILC2s are positively correlated with M2 macrophages and blood eosinophil


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counts, indicating that they can determine asthma phenotypes by regulating macrophage polarization (66). Further investigations are needed to understand the interplay between ILC1/ILC3 and AECs/macrophages.

## BIOLOGICS FOR THE TREATMENT OF SA

To date, various biologics have been approved as treatment options to target specific inflammatory pathways in the pathogenesis of SA (**Fig. 2**). Based on the clinical studies of each biologic (67-79), we discussed its mechanism of action and clinical efficacy (for both type 2 and non-type 2 inflammation) in asthma (**Table 1**).

### Anti-IgE Ab

IgE released by B cells in response to allergens is essential for inducing immune cell activation, but omalizumab could reduce IgE-mediated responses as well as eosinophil counts in the airways by the following mechanism (80,81). Omalizumab is recognized as the first humanized mAb for managing allergic asthma inadequately controlled with the standard treatment by inhibiting IgE binding to its high-affinity receptor on mast cells and basophils (82). In addition to severe allergic asthma, the function of omalizumab in type 2-low and nonatopic asthma has been demonstrated (83,84), implying a possible role of omalizumab in various asthma phenotypes of SA. However, efforts to better understand each patient's condition are necessary to predict which patients would have the greatest efficacy, although omalizumab has shown many potential benefits and long-term safety in various aspects.

### Anti-IL-5 Ab

Two anti–IL-5 antibodies, including mepolizumab, reslizumab, as well as one anti-IL-5 receptor Ab, benralizumab are currently available for the treatment of severe eosinophilic

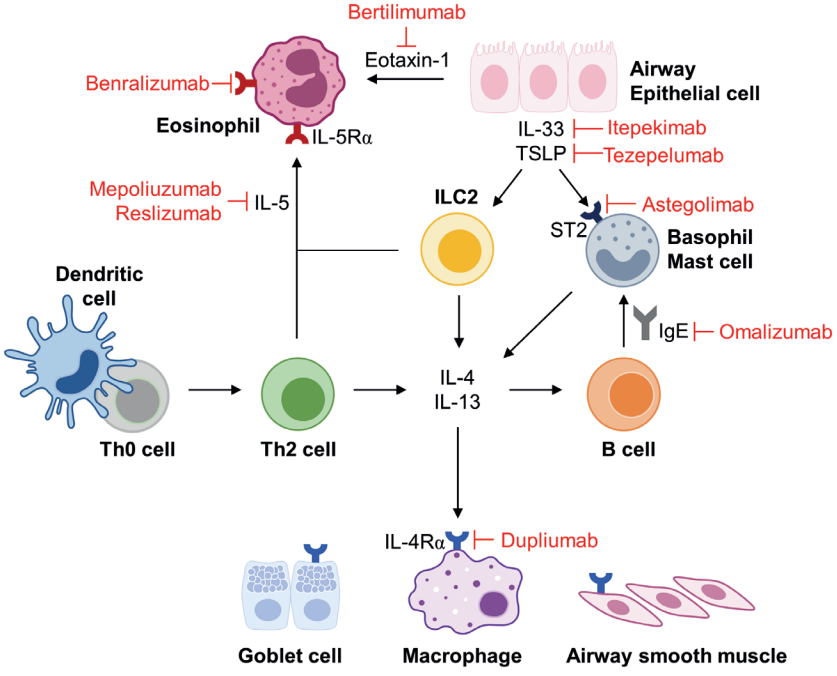


**Figure 2.** Potential biological targets in type 2 asthma.
IL-4Rα, interleukin 4 receptor subunit alpha; IL-5Rα, interleukin 5 receptor subunit alpha.


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**Table 1.** Summary of specific mechanisms and clinical efficacy of current biologics in asthma

| Biologics | Target | Mechanism of action | Anticipated effect | Clinical application | Ref. |
|---|---|---|---|---|---|
| Omalizumab | IgE | Inhibits free IgE from binding to FcεRI on mast cells and basophils | · Reduction in asthma exacerbation<br>· Improvement in $FEV_1$<br>· Improvement in QoL<br>· ICS/OCS-sparing effect | · Moderate/severe allergic asthma uncontrolled with step 4/5 treatment<br>· Childhood-onset asthma | (67,68) |
| Mepolizumab | IL-5 | Prevents IL-5 from binding to its receptor | · Reduction in severe exacerbation<br>· Improvement in QoL<br>· OCS-sparing effect | · Severe asthma with high blood eosinophils (≥ 150/μl) | (68-70) |
| Reslizumab | IL-5 | Prevents IL-5 from binding to its receptor | · Reduction in asthma exacerbation<br>· Improvement in $FEV_1$<br>· Improvement in QoL | · Adult onset, severe eosinophilic asthma with high blood eosinophils (≥ 400/μl) | (71) |
| Benarlizumab | IL-5Rα | Targets the α subunit of IL-5R on eosinophils for their apoptosis by ADCC | · Reduction in blood eosinophil count<br>· Reduction in asthma exacerbation<br>· Improvement in $FEV_1$<br>· OCS-sparing effect | · Severe asthma with high blood eosinophils (≥ 300/μl) | (72-74) |
| Dupilumab | IL-4R | Targets the α subunit of IL-4R for blocking IL-4 and IL-13 signaling pathway | · Reduction in blood eosinophil count<br>· Reduction in severe exacerbation<br>· Improvement in $FEV_1$<br>· Improvement in QoL<br>· OCS-sparing effect | · Severe eosinophilic/type 2 asthma with high blood eosinophils (≥ 150/μl) or FeNO (≥ 25 ppb) | (68,75) |
| Itepekimab | IL-33 | Inhibits IL-33 from binding to its receptor (ST2) | · Reduction in blood eosinophil count and total IgE levels<br>· Improvement in $FEV_1$ and FeNO<br>· Improvement in QoL | · Moderate-to-severe asthma (more effective in combination with dupilumab in type 2 asthma) | (76) |
| Astegolimab | IL-33R (ST2) | Blocks the receptor of IL-33 (ST2) | · Reduction in asthma exacerbation<br>· Improvement in $FEV_1$ | · Type 2-low asthma with low blood eosinophils (< 300 μl) | (77) |
| Tezepelumab | TSLP | Prevents TSLP from binding to its receptor | · Reduction in blood eosinophil count and total IgE levels<br>· Reduction in asthma exacerbation<br>· Improvement in $FEV_1$ and FeNO<br>· Improvement in QoL | · Severe asthma with severe exacerbation (regardless of high or low T2 markers) | (78,79) |

ADCC, antibody-dependent cellular cytotoxicity; FcεRI, Fc epsilon receptor I alpha; $FEV_1$, forced expiratory volume in 1 second; ICS, inhaled corticosteroids; OCS, oral corticosteroids; ppb, parts per billion; QoL, quality of life; ST2, suppression of tumorigenicity 2.

asthma. All these biologics have been shown to be effective in managing type 2 asthma with eosinophilic inflammation; however, they are different in mechanisms of action as well as in pharmacokinetic and pharmacodynamic profiles.

Mepolizumab is a humanized mAb against IL-5 and targets severe eosinophilic asthma with higher blood eosinophil count (>150 cells/μl). The efficacy and safety of mepolizumab have been validated by various randomized controlled trials. It improves clinical outcomes, such as reduction in blood eosinophil counts, the frequency of asthma exacerbation, and oral corticosteroids (OCS) use as well as improvement in lung function and quality of life (85,86). Especially, its effect is greater in asthmatic patients with high blood eosinophil count, low body mass index, or no smoking experience. Therefore, it is recommended for the treatment of type 2 SA (with higher blood eosinophil counts) as a therapeutic option at step 5 of the recent Global Initiative for Asthma (GINA) guideline (87).

Reslizumab is a humanized anti-IL-5 mAb administered intravenously for patients with eosinophilic asthma who are in uncontrolled status even on high-dose ICS and additional controllers. Randomized controlled trials demonstrated that this drug could reduce the frequency of asthma exacerbation, short-acting β-agonist/OCS use as well as improve lung functions. In particular, the effect of reslizumab is prominent in asthmatic patients with high blood eosinophil counts (>400 cells/μl). Therefore, it is recommended as a therapeutic option for patients with severe eosinophilic asthma at step 5 of the recent GINA guideline (88-90).

Benralizumab targets the α subunit of the IL-5 receptor expressed on eosinophils and basophils and induces their apoptosis by Ab-dependent cell-mediated cytotoxicity. Thus, it has strengths of directly killing eosinophils resident in tissues as well as circulating in blood. Several studies have shown that benralizumb reduces blood eosinophil rapider and more effectively than other anti-IL-5 biologics. Moreover, it decreases asthma exacerbation rate and OCS dose with lung function improvement in patients with severe eosinophilic asthma (91). However, the evidence for the safety of long-term use is still controversial because of its immunogenicity response and strong effect on eosinophil depletion (85,92). Current GINA guideline recommends this drug for patients with severe eosinophilic asthma with higher blood eosinophil counts (>300 cells/μl) at the step 5.

### Anti-IL-4/IL-13 Ab

Dupilumab is a humanized mAb targeting the α subunit of the IL-4 receptor, which blocks signaling cascade induced by both IL-4 and IL-13 involving IgE production, immune cell recruitment, goblet cell hyperplasia, and airway remodeling in SA (93). Randomized clinical trials found that asthmatic patients who received dupilumab have significantly lower asthma exacerbation rates, improved lung function, and better asthma controls. Although dupilumab has some side effects, including injection site reaction and blood eosinophilia, greater efficacy has been shown in patients with higher baseline eosinophil counts and FeNO values, representing type 2 phenotype (75). Furthermore, inhaled recombinant IL-4 receptor improved lung function and asthmatic symptoms even after corticosteroid withdrawal in persistent asthma (94). Although these biologics may have advantages in that it blocks IL-4/IL-13 which reduce type 2 airway inflammation in AECs, further understanding on their mechanisms and any biomarkers predicting favorable responders are essential to elucidate the greatest benefit from a specific biologic for each patient (95-97).

### Anti-IL-33/TSLP Ab

Currently, the development of new biologics targeting epithelial cell-derived cytokines (known as alarmins), including IL-33 and TSLP, is undergoing to regulate alternative pathophysiological pathways, because AECs are major targets as well as immune cells in patients having type 2 or non-type 2 asthma. These biologics are involved in the upstream of immune responses, affecting both innate and adaptive immunity in the airways. Itepekimab is a humanized mAb against IL-33 which binds to the IL-33 receptor complex, regulating downstream signaling for activation of immune systems. After treatment with itepekimab, improved lung function in patients with moderate-to-severe asthma has been noted in a phase 2 trial (76). Furthermore, astegolimab, a novel mAb targeting the receptor for IL-33 (suppression of tumorigenicity 2 [ST2]), was found to be effective in uncontrolled SA. In phase 2 trials, its subcutaneous administration reduced asthma exacerbation rates and improved lung functions with safety in patients with type 2-low asthma (showing low blood eosinophil counts, <300 cells/μl) (77). Tezepelumab is a humanized mAb that binds to TSLP, inhibiting its interaction with the TSLP receptor complex (98). In a phase 2 trial, tezepelumab showed significant reduction in asthma exacerbation rates, IgE levels and FeNO values in adult asthmatic patients, regardless of baseline eosinophil counts (78). Moreover, patients with severe uncontrolled asthma who received tezepelumab also showed lower asthma exacerbation rates, but higher lung function with health-related quality of life in a phase 3 trial (79). In addition, a recent clinical trial have shown the effect of an inhaled anti-TSLP (CSJ117) on reducing bronchoconstriction and sputum eosinophils as well as on improving FeNO levels in patients with allergic asthma (99). These therapeutic agents most likely have functions in patients with type 2 asthma; however, it is expected to be useful in those without evidence of eosinophilic inflammation.


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### New potential biologics

Eotaxin-1 is known as a chemoattractant for eosinophils, inducing their activation and recruitment into the inflamed site. Bertilimumab, a human mAb against eotaxin-1, is developed as a novel therapeutic biologic for bullous pemphigoid which is an autoimmune skin disease characterized by dermal and blood eosinophilia. Recently, its efficacy and safety have been proved in a phase 2a trial (NCT02226146), reducing serum ECP levels and disease severity with a steroid-sparing effect. Based on these results, bertilimumab is under current studies for allergic disease, such as atopic dermatitis, rhinitis, and asthma. Considering higher blood concentrations of eotaxin-1 in patients with asthma, bertilimumab can be a promising biologic for severe eosinophilic asthma with further studies for its clinical efficacy (100,101).

## FUTURE DIRECTIONS

SA patients still suffer from serious modality and high mortality. They are broadly divided into type 2 and non-type 2 asthma; however, this classification may not be appropriate given the diversity of its phenotypes. Therefore, ongoing studies on dissecting the underlying immunological mechanisms of SA will enable us to further identify multiple phenotypes/endotypes of SA, an essential step to achieving the precision medicine. The major goal in the management of SA is to prevent asthma exacerbation and lung function decline, which is possible by modifying underlying inflammatory mechanisms. Recent biologics (single or combined use) have some benefits for modifying disease properties. Further research on understanding immunological mechanisms and validating new therapeutic targets are expected to address medical unmet needs in SA.

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