

Biologic Targeting: New and Effective Therapeutic Approaches against Severe Asthma

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Asthma is defined as a chronic airway inflammation characterized by bronchial hyperresponsiveness, reversible restriction in airflow, and structural remodeling of airway. Patients often present with coughing, wheezing, dyspnea, and chest tightness.^[1] Applications of inhaled corticosteroid (ICS) and long-acting β_2 agonist (LABA) relieve most of the symptoms in the majority of asthma patients, yet an estimated 3.6% of the patients fail to benefit from existing treatment regimens, which increases the patient burden and negatively affects their life quality.^[2] In the process of asthma, IgE plays an important role. As the first monoclonal anti-IgE antibody, omalizumab has been confirmed to improve the asthma symptom score, reduce the acute attack of asthma, lower the dosage of oral or inhaled glucocorticoid, and ameliorate life quality of asthma patients. Omalizumab marks the beginning of a new era in treating severe asthma. Besides IgE, eosinophils are also intimately involved in the pathogenesis of asthma and are associated with disease severity, exacerbation frequency, and mortality. Many of the proinflammatory factors, such as interleukin (IL)-5, IL-4, IL-13, and IL-17, play important roles in the pathological processes of the maturation, activation, survival, and recruitment of eosinophils in severe asthma [Figure 1]. These can impact inflammation and structural changes in the respiratory tract. Therefore, it is plausible to block key factors that contribute to eosinophilia in the treatment of severe asthma.

ANTI-INTERLEUKIN-5/INTERLEUKIN-5 RECEPTOR ALPHA MONOCLONAL ANTIBODY

Researchers have found that IL-5 plays a significant part in eosinophil-mediated inflammatory reactions through its involvement in the differentiation of eosinophils from bone

marrow.^[3] Accordingly, biotherapeutics targeting IL-5/IL-5 receptor alpha (IL-5R α) such as mepolizumab, reslizumab, and benralizumab were developed.

Mepolizumab was the first anti-IL-5 monoclonal antibody and was approved by the Food and Drug Administration (FDA) as an add-on treatment for asthma in 2015. In some cases, the persistence of high eosinophil numbers in circulation requires high-dose corticosteroid treatment. Mepolizumab can reduce the number of eosinophils, thereby relieving symptoms in severe asthma patients and decreasing the required dosage of corticosteroids, but it has no significant effect on pulmonary function. In general, the number of eosinophils in circulation increases after an airway-allergen challenge, but treatment with mepolizumab prevents this increase. Kelly and colleagues found that the levels of surface IL-3R α protein and mRNA expression were reduced after administering mepolizumab. In addition, surface β_c decreased, and there was a tendency for surface IL-5R α to increase. However, there were no obvious changes in the levels of the IL-5-inducible activation markers including CD69, CD44, and CD23 or in the level of the receptors for the IL-5-family of cytokines (IL-5, IL-3, and granulocyte-macrophage colony-stimulating factor) after Mepolizum administration, suggesting these cells remain functional. These findings may explain why asthma exacerbations do not enter complete remission after IL-5 neutralization.^[4]

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Another anti-IL-5 monoclonal antibody is reslizumab, which decreases the sputum eosinophil number in patients who have been treated with mepolizumab for at least 1 year although it does not decrease the eosinophil number. However, forced expiratory volume in the 1st s (FEV1) and Asthma Control Questionnaire (ACQ-5) scores were significantly improved with weight-adjusted reslizumab therapy, and it has been suggested that the sputum levels of IL-5 and anti-eosinophil peroxidase IgG may be predictive of the anti-IL-5 therapy response. The strategy of weight-adjusted reslizumab thus seems to be more effective than fixed-dose mepolizumab in reducing airway eosinophil counts and should improve asthma control in prednisone-dependent patients.^[5]

Benralizumab is an anti-eosinophilic, anti-IL-5 receptor α monoclonal antibody that effectively reduces the eosinophil count in circulation and the frequency of asthma exacerbations. More importantly, benralizumab appears to not only reduce asthma exacerbations in eosinophilic asthma (baseline blood eosinophils >300 cells/ μ l) but compared with placebo, also reduce exacerbation in noneosinophilic asthma (baseline blood eosinophils <300 cells/ μ l) patients, who currently require high-dosage ICS plus LABA for exacerbation control.^[6] In a 28-week randomized controlled trial, researchers found that compared with placebo, both high (every 4 weeks) and low (every 8 weeks) dosages of benralizumab reduced the median final oral glucocorticoid dosages. The annual asthma exacerbation rate was also reduced in the benralizumab subgroup.^[7] However, benralizumab had no clinically significant effects on asthma symptom indices such as the FEV1, ACQ, and asthma quality life questionnaire scores. Thus the random control trials on the curative effects of benralizumab have been inconsistent,^[8] further studies on whether it can improve patients' lung function are required.

ANTI-INTERLEUKIN-13 MONOCLONAL ANTIBODY AND ANTI-INTERLEUKIN-4 RECEPTOR MONOCLONAL ANTIBODY

IL-13 has attracted particular attention as a therapeutic target for the asthma treatment, as it not only induces airway hyperresponsiveness in animal models of asthma, but also leads to some of the structural changes caused by chronic airway inflammation, including goblet cell hyperplasia, airway smooth muscle proliferation, and subepithelial fibrosis, the typical pathological manifestations of asthma.^[9]

As the monoclonal antibody that targets IL-13, tralokinumab improved lung function and decreased the use of beta-agonists, but no improvement was seen in the symptoms of adults with moderate-to-severe asthma.^[10] Lebrikizumab, another anti-IL-13 monoclonal antibody, was only associated with improvements in lung function in adults with asthma that was inadequately controlled with ICS therapy.^[11] Both two drugs are still under Phase II clinical trial.

Although the IL-13 monoclonal antibodies seem to only improve lung function, dupilumab, an anti-IL-4 receptor

human monoclonal antibody, blocks transduction signals activated by IL-13 and IL-4, providing more benefits to patients with the Th2-high phenotype. IL-4 plays a critical role in the differentiation of Th2 cells from uncommitted Th0 cells, and it may be important in the initial sensitization to allergens. It is also important for switching B cells to produce IgG and IgE.^[3] Combined with the role of IL-13 in asthma pathogenesis, dupilumab decreases Th2-associated biomarkers. When used as add-on therapy to ICS and LABA, dupilumab improved FEV1 levels, morning asthma-symptom scores, and ACQ-5 scores. Dupilumab also reduces risk by lowering the annualized severe exacerbation-event rate in patients with both high and low eosinophil numbers, and for the majority of patients, there was little or no change in the peripheral blood eosinophil levels.^[12]

ANTI-INTERLEUKIN-17 ALPHA MONOCLONAL ANTIBODY

In addition to the Th-2 related cytokines, there are also some other cytokines that can regulate the pathogenesis of severe asthma. Th-17 is another T-cell type, which secretes IL-17 to affect the pathogenesis of several inflammatory diseases, including plaque psoriasis, ankylosing spondylitis, psoriatic arthritis, and asthma. IL-17 seems to contribute to neutrophilic accumulation in the airway, resulting in related growth factors and chemokines, makes corticosteroids resistant to the treatment. In addition, IL-17 mRNA levels positively correlate with IL-5 mRNA levels in the sputum from asthmatic patients. These data may provide a potential clue about the association of IL-17 with Th2-mediated eosinophilic airway inflammation in asthma,^[13] and these data also explain why monoclonal antibodies to IL-17 were expected to have a positive effect on several of inflammatory diseases.

Secukinumab, a human anti-IL-17A monoclonal antibody, has been shown to be effective in the treatment of moderate-to-severe plaque psoriasis and ankylosing spondylitis, as well as in multiple myeloma in a mouse model and *in vitro* studies.^[14,15] However, none of the expected results occurred in the treatment of severe asthma. Secukinumab was evaluated in the ozone-induced airway-neutrophilia model of lung inflammation. After a subsequent ozone challenge, no significant differences were found in the sputum neutrophil number between the treatment or placebo groups.^[16] Another anti-IL-17A monoclonal antibody, brodalumab, had no effect in a population with inadequately controlled moderate-to-severe asthma. However, a high bronchodilator reversibility subgroup may have had a meaningful response to the treatment, which supports further study of brodalumab for this specific phenotype of severe asthma.^[17]

ANTI-THYMIC STROMAL LYMPHOPOIETIN MONOCLONAL ANTIBODY

Thymic stromal lymphopoietin (TSLP) is a cytokine that influences the differentiation of B lymphocytes and the

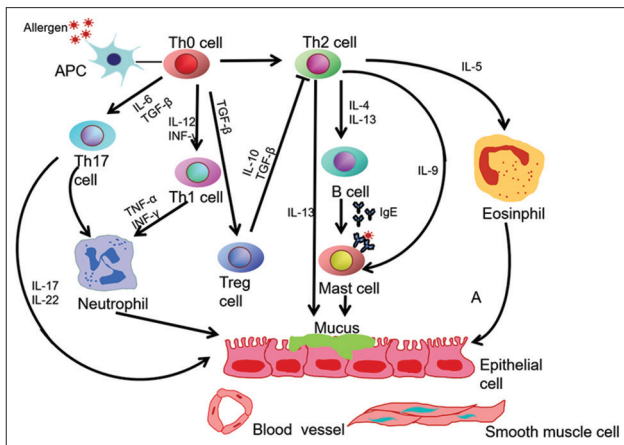


Figure 1: Pathobiology of cytokines in the allergic inflammation.

proliferation of T lymphocyte. Studies have shown that TSLP activates dendritic cells and induces the biochemical factors that initiate the CD4⁺ T cell transform to Th2 cells and then release the Th2-related biochemical factors, resulting in allergic inflammation [Figure 2]. Tezepelumab, a human monoclonal antibody for TSLP, is at Phase II, randomized, double-blind, placebo-controlled trial stage in patients suffering from severe refractory asthma. In this clinical trial, three different dosages of tezepelumab reduced the annualized asthma exacerbation rates. The effect of the tezepelumab appeared to be the same in the population regardless of the patient's number of eosinophils.^[18] Therefore, tezepelumab is expected to be a new strategy for effectively treating severe refractory asthma.

BCL-2 INHIBITOR

In addition to antibodies to cytokines, some new drugs have been developed to control severe resistant asthma. We know that both eosinophilic and neutrophilic airway inflammation can induce resistance to corticosteroid treatment, thus granulocyte clearance seems to be a key point in curing severe refractory asthma. Our group found that the Bcl-2 inhibitors ABT-737 and ABT-199 can induce apoptosis in immune cells, including eosinophils, neutrophils, Th2 cells, and Th17 cells. In addition, the Bcl-2 inhibitors were more effective than steroids at inducing granulocyte apoptosis in the blood granulocytes from patients with severe asthma. Consequently, the Bcl-2 inhibitors ABT-737 and ABT-199 should reduce the number of neutrophils and eosinophils available in the airway.^[19] These findings provide us with a new way of thinking about and direction for treating severe refractory asthma.

In general, most of the biological therapies can relieve the symptoms of severe asthma, improve the quality of life, and they are expected as the add-on therapy to the currently available treatments, but some drugs still have their deficiency. For example, anti-IL-5/IL-5R α monoclonal antibodies have no effect on improving lung function; anti-IL-17 monoclonal antibodies are not able to achieve predictive effects for the severe asthma treatment. On the

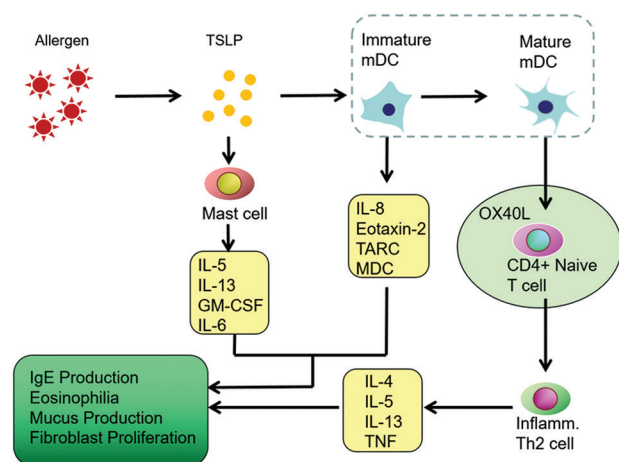


Figure 2: The mechanism of TSLP inducing allergic inflammation. TSLP: Thymic stromal lymphopoietin; mDC: Myeloid dendritic cell; TNF: Tumor necrosis factor; TARC: Thymus and activation-regulated chemokine; MDC: Macrophage-derived chemokine; IL: Interleukin.

other hand, there are some inspiring discoveries, such as dupilumab and tezepelumab seem to have good effects on patients with both high and low eosinophil numbers; our group found Bcl-2 inhibitors can reduce the inflammation in the airway. This may give us new directions in the treatment of severe asthma.

Among these novel biological therapeutic approaches, several drugs, including mepolizumab, reslizumab, and benralizumab, have been approved by the FDA for treating severe refractory asthma, while some other monoclonal antibodies are still under clinical trials. We must consider how to choose the appropriate drugs according to the different phenotypes of severe asthma to achieve the optimal therapeutic effect and reduce side effects. Hopefully, in the future, more drugs will be developed to benefit these patients.

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