



Invited Review Article

Current summary of clinical studies on anti-TSLP antibody, Tezepelumab, in asthma

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ABSTRACT

Thymic stromal lymphopoietin (TSLP) is an epithelial cell-derived cytokine that plays a vital role in the induction of type 2 inflammation via both innate and acquired immune cascades. Tezepelumab, a human IgG2 monoclonal antibody that inhibits the binding of TSLP to the TSLP receptor, is the latest biologic for asthma. To evaluate the efficacy and mechanism of tezepelumab in asthma, the PATHWAY, NAVIGATOR, NOZOMI, UPSTREAM, CASCADE, SOURCE, and DESTINATION studies have been conducted. These results suggested that tezepelumab is a broad-target biologic, which is expected to be effective in patients with poorly controlled moderate to severe asthma regardless of the phenotype, although its efficacy in oral corticosteroids-dependent asthma, biological mechanism in non-type 2 phenotype, and long-term safety remain unknown. In this review, we summarize the results of clinical trials of tezepelumab in asthma and discuss the differences between tezepelumab and other biologics.

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Introduction

Allergic diseases are initiated by antigen-presenting cells that capture allergens and induce allergen-specific Th2 cells in the regional lymph nodes. Th2 cells produce type 2 cytokines, such as interleukin (IL)-4, IL-5, and IL-13, which play a critical role in the induction of asthma. For example, IL-4 induces IgE antibody production by promoting B cell class switch, IL-5 activates eosinophils, and IL-13 induces goblet cell hyperplasia and airway remodeling. Furthermore, IgE antibodies bind to FcεRI with allergens on the surface of mast cells and basophils, causing the release of chemical mediators. In recent years, it has been reported that group 2 innate lymphoid cells (ILC2s), which are directly activated by epithelial cell-derived cytokines, produce large amounts of type 2 cytokines, including IL-5 and IL-13, and are also involved in the pathogenesis of asthma, in addition to the conventional acquired immunity-mediated allergic inflammation.¹ Thus, the pathogenesis of asthma is now considered to be formed by a complex network of various immune cells.

The biologics that have been clinically used for asthma are anti-IgE antibodies, anti-IL-5 antibodies, anti-IL-5 receptor (anti-IL-5R)

antibodies, and anti-IL-4 receptor alpha (anti-IL-4Rα) antibodies, all of which inhibit one or two specific cytokines or IgE antibodies, and thus only partly suppress the complex type 2 inflammation cascade. Therefore, to treat asthma more effectively, biologics must target more upstream molecules in the pathophysiological pathway of asthma.

Thymic stromal lymphopoietin (TSLP) is a lymphocyte-stimulating cytokine, identified in thymic stromal cells of mice in 1994.² TSLP is mainly expressed in epithelial cells of barrier surfaces, such as skin, airways, and gastrointestinal tract, that help the body to sense the outside world. TSLP is also produced by fibroblasts and dendritic cells in response to a variety of external factors. The functions of TSLP are diverse and include the induction of Th2 cells by increasing OX40L expression in dendritic cells, promotion of differentiation into Th2 cells by acting on CD4⁺ T cells, induction of IL-4 production by activating basophils, activation of ILC2s and induction of corticosteroid resistance, and various other functions that form the basis of asthma pathophysiology. Therefore, inhibition of TSLP could simultaneously suppress multiple allergic cascades and is attracting attention as a new therapeutic target for asthma.^{3–5}

Tezepelumab is a human IgG2 monoclonal antibody, that inhibits the binding of TSLP to the TSLP receptor, developed by AstraZeneca and Amgen. It is the latest biologic for treatment of asthma, approved by the FDA as of December 2021. In Japan, it was approved for patients with moderate to severe uncontrolled asthma in September 2022. This review summarizes the clinical

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trials with tezepelumab that have been reported to date (Table 1) and discusses how it differs from other biologics.

Phase 1 study evaluating the efficacy of tezepelumab in asthma

In 2014, a phase 1b randomized, double-blind, controlled trial that evaluated the efficacy of tezepelumab in patients with asthma was reported.⁶ In this study, 31 patients with stable mild atopic asthma (16 in the AMG-157 (tezepelumab) group vs 15 in the placebo group) were recruited to evaluate whether tezepelumab can prevent the decline in pulmonary function, forced expiratory volume in 1 s (FEV₁), after allergen inhalation. Generally, patients with asthma demonstrate a bimodal reduction in pulmonary function caused by allergen inhalation. After allergen inhalation, IgE-dependent release of chemical mediators (such as histamine and PGD₂) from basophils and mast cells cause immediate airway narrowing, followed by delayed airway narrowing several hours later by leukotrienes produced by eosinophils infiltrating the airways. In this study, tezepelumab 700 mg was administered intravenously on days 1, 29, and 57, and allergen inhalation was performed on days 42 and 84. Tezepelumab significantly inhibited the decline of FEV₁ in both immediate (within 2 h after inhalation) and delayed (3–7 h after inhalation) reactions on days 42 and 84. In addition, tezepelumab was shown to inhibit methacholine-induced airway hyperresponsiveness. These results suggest that TSLP plays an important role in allergen-induced airway narrowing in asthma and that tezepelumab can effectively prevent asthma exacerbation. In addition, the number of eosinophils in the peripheral blood and sputum, and fractional exhaled nitric oxide (FeNO) levels were significantly decreased in the tezepelumab group, suggesting that tezepelumab broadly inhibits type 2 cytokines, including IL-4, IL-5, and IL-13.⁶

Phase 2 study evaluating the efficacy of tezepelumab in asthma

Next, the PATHWAY study, a phase 2b multicenter, randomized, double-blind study evaluating the efficacy and dosage of tezepelumab in patients with asthma was reported in 2017.⁷ This study enrolled patients with poorly controlled asthma who had experienced at least two episodes of asthma exacerbations within the past year despite treatment with a combination of a medium- or high-dose inhaled corticosteroid (fluticasone equivalent ≥ 250 μ g/day) and a long-acting beta2-stimulant. Five hundred and fifty patients were randomly assigned to groups with different doses of subcutaneous tezepelumab injection: low-dose (70 mg every 4 weeks), medium-dose (210 mg every 4 weeks), high-dose (280 mg every two weeks), and placebo (every two weeks) for 52 weeks. The annual asthma exacerbation rate (AAER), the primary endpoint, were 0.27 in the low-dose group, 0.20 in the medium-dose group, and 0.23 in the high-dose group, all of which were significantly lower compared with 0.72 in the placebo group. In particular, the AAER reduction was pronounced in patients with asthma taking high doses of inhaled corticosteroids.

The PATHWAY study included various stratification analyses. Both groups with high (≥ 250 cells/ μ L) and low (< 250 cells/ μ L) blood eosinophil counts showed significant inhibition of exacerbation. Comparison of the high FeNO (≥ 24 ppb) and low FeNO (< 24 ppb) groups showed that tezepelumab reduced AAERs equally. However, there was no statistically significant difference between tezepelumab and the placebo in the low FeNO group since the placebo group also showed low AAER. Furthermore, in this study, “Th2 status high” was defined as a total serum IgE level of 100 IU/mL or higher and blood eosinophil counts of 140 cells/ μ L or

higher, while “Th2 status low” was defined as a patient who did not meet the above criteria. Tezepelumab reduced AAER in both the “Th2 status high” and “Th2 status low” groups. These results suggest that low to high doses of tezepelumab can suppress AAER in patients with poorly controlled asthma, regardless of blood eosinophil count, FeNO, or Th2 status.

As the secondary endpoint, the prebronchodilator FEV₁ at 52 weeks was significantly improved in the tezepelumab group compared with the placebo group (differences from the placebo are as follows: low-dose group +120 mL, medium-dose group +130 mL, high-dose group +150 mL). ACQ-6, a measure of asthma control, and AQLQ, a measure of the asthma-related quality of life, also showed improvement in the tezepelumab group. Similar to the phase 1b study results, blood eosinophil counts and FeNO were reduced after 4 weeks of tezepelumab treatment, while serum total IgE levels gradually decreased after 12–20 weeks of tezepelumab treatment. There was no apparent difference in the frequency of adverse events between the tezepelumab and placebo groups. However, serious reactions in the tezepelumab group included pneumonia and stroke in one patient, and Guillain-Barré syndrome in another patient. There were no anaphylactic reactions resulting from tezepelumab administration.⁷

Several post-hoc analyses were performed based on the PATHWAY study. Tezepelumab was reported to decrease emergency room visits and shorten the length of stay after emergency hospitalization.⁸ Patients treated with tezepelumab significantly improved their ACQ-6 and AQLQ(S)+12 scores.⁹ Furthermore, it was also reported that tezepelumab suppressed asthma exacerbations, regardless of the presence or absence of eosinophilic sinusitis (nasal polyps),¹⁰ and perennial allergies,¹¹ and that the efficacy of tezepelumab was independent of the season.¹² In terms of biomarkers, tezepelumab reduced blood eosinophil counts, FeNO, serum IgE, IL-5, IL-13, periostin, thymus and activation-regulated chemokine (TARC), and TSLP at 52 weeks.¹³ In particular, IL-5 and IL-13 levels were reduced to levels comparable to those in healthy participants after 52 weeks of tezepelumab treatment.¹⁴

Phase 3 study evaluating the efficacy of tezepelumab in asthma

The NAVIGATOR study is a phase 3 randomized, double-blind, placebo-controlled study evaluating the efficacy of tezepelumab, reported in 2021.¹⁵ The NAVIGATOR study enrolled patients with more severe asthma than those in the PATHWAY study; patients with poorly controlled severe asthma who had experienced two or more episodes of asthma exacerbations within the past year despite treatment with medium- or high-dose inhaled corticosteroids (≥ 500 μ g/day fluticasone equivalent), in combination with one or more long-term asthma controllers, including oral corticosteroids, were included. A total of 1061 patients were randomly assigned in 1:1 ratio, to receive a 210 mg dose of tezepelumab subcutaneously, the mid-dose in the PATHWAY study, or placebo every 4 weeks for 52 weeks. The study's primary endpoints were the AAER in the overall population and the subgroup with eosinophil counts < 300 cells/ μ L. Tezepelumab showed statistically significant inhibition of the AAER in both groups: AAER was 0.93 in the tezepelumab group and 2.10 in the placebo group in the overall population, and 1.02 in the tezepelumab group and 1.73 in the placebo group in the patients with low eosinophil counts.

As secondary endpoints, tezepelumab group improved prebronchodilator FEV₁ at 52 weeks by +130 mL compared to the placebo group, which is comparable to the PATHWAY study result. In addition, ACQ-6, AQLQ, and asthma symptom diary (ASD) scores were significantly improved in the tezepelumab group. This study stratified the baseline eosinophil counts more finely, and

Table 1
Clinical studies on tezepelumab in asthma.

Trial	Phase	Purpose	Number of participants	Subjects	Primary endpoint	Main result	Conclusion
NCT01405963 ⁶	1b	Test the hypothesis that tezepelumab suppresses allergen-induced bronchoconstriction in patients with mild atopic asthma.	31	Mild atopic asthma	Late asthmatic reaction after allergen inhalation	Improved maximum reduction in FEV ₁ , minimum FEV ₁ , and Area under the curve (AUC) for time-adjusted minimum FEV ₁	Reduced allergen-induced bronchoconstriction and airway inflammation
UPSTREAM ¹⁸	2	Evaluate mechanisms through which tezepelumab suppresses airway irritability and airway inflammation	40	Adult asthmatic patients receiving ICS ($\pm$ LABA)	Mannitol PD ₁₅	Improved mannitol PD ₁₅ , but not significantly. Eosinophil counts in airway tissue, BAL, sputum, and blood decreased.	Airway irritability was improved, and eosinophils reduced in airway tissues
PATHWAY ⁷	2b	Evaluate the efficacy of tezepelumab in moderate to severe asthma patients	550	Uncontrolled moderate to severe asthma	Annual asthma exacerbation rate (AAER)	AAER, FEV ₁ , ACQ-6, and AQLQ significantly improved	Reduced AAER regardless of peripheral blood eosinophil counts and FeNO
CASCADE ¹⁹	2	Evaluate mechanisms through which tezepelumab suppresses airway irritability and airway inflammation	116	Uncontrolled moderate to severe asthma	Number of inflammatory cells of the airway submucosa on bronchoscopic biopsy	Improved mannitol-induced airway hyperresponsiveness and decreased airway submucosal eosinophil counts	Airway irritability improved and the number of eosinophils in the airway submucosa decreased
NAVIGATOR ¹⁵	3	Evaluate the efficacy and safety of tezepelumab in uncontrolled severe asthma patients	1061	Uncontrolled moderate to severe asthma	AAER in the overall group and peripheral blood eosinophil counts <300/ μ L group	Significant improvement in AAER, FEV ₁ , ACQ-6, AQLQ, ASD	Reduced AAER regardless of eosinophil counts and FeNO
NOZOMI ¹⁷	3	Evaluate the long-term safety of tezepelumab in Japanese patients with asthma	65	Uncontrolled moderate to severe asthma	Adverse event rates	No new adverse events	Safety and efficacy of tezepelumab were confirmed in Japanese patients with asthma.
DESTINATION ²⁵	3	Evaluate the long-term safety and tolerability of tezepelumab	966	Uncontrolled moderate to severe asthma	Adverse event rates	N/A	N/A
SOURCE ²¹	3	Evaluate the rate of OCS reduction in OCS-dependent asthma patients	150	OCS-dependent asthma	Reduction rate in OCS dose	No significant difference in OCS dose reduction rate was observed, but pre-BD FEV ₁ , AAER at 48 weeks, number of asthma exacerbations, lung function, QOL, blood eosinophil count, FeNO, and serum total IgE concentration improved.	Oral corticosteroid dose reduction rate was not significantly different. A reduction in OCS dose and improvement of AAER, FEV ₁ , and ACQ-6 were observed in patients with blood eosinophil counts of 150 cells/ μ L or higher.

tezepelumab showed significant inhibition of AAER in all subgroups, including the subgroup with blood eosinophil counts <150 cells/ μ L. Furthermore, tezepelumab reduced AAER in the groups of patients with low FeNO (<25 ppb), and regardless of the sensitization to perennial allergens. However, tezepelumab is more beneficial for patients with high eosinophils and FeNO; improvement of lung function, ACQ-6, and AQLQ was not significant in the patients with low blood eosinophil counts (<150 cells/ μ L). Consistent with previous studies, significant suppression of blood eosinophil counts and FeNO levels were observed early (after two weeks) after tezepelumab treatment. In contrast, serum total IgE levels showed a gradual decrease after 12 weeks of treatment, similar to the results of the PATHWAY study. Both tezepelumab and placebo groups experienced similar adverse events; the most common were nasopharyngitis, upper respiratory tract inflammation, and headaches. Guillain-Barré syndrome, observed in the PATHWAY study, was not observed in this study, and anaphylactic reactions were not observed.

Taken together, the results of these clinical trials have demonstrated that tezepelumab improved AAER in poorly controlled patients with asthma who had at least two asthma exacerbations episodes per year despite treatment with a combination of a medium- or high-dose inhaled corticosteroid (fluticasone equivalent ≥ 250 μ g/day) and other controllers (treatment step 3 or more in the Japanese guidelines for adult asthma¹⁶). This improvement of AAER was regardless of biomarkers, including blood eosinophil counts, FeNO, or sensitization to perennial allergens. Reflecting the involvement of TSLP in multiple allergic cascades, tezepelumab broadly suppressed type 2 inflammation, including blood eosinophil counts, FeNO, and serum IgE levels. In addition, the onset of the effects of tezepelumab was rapid, and reductions in eosinophils and FeNO were observed after only two weeks of tezepelumab treatment. Interestingly, in the phase 1b study,⁶ the immediate asthmatic response to allergen inhalation suppressed after 42 days of the first dose of tezepelumab, when IgE levels were not expected to have decreased (indeed, no reduction in serum IgE levels was reported in the phase 1b study). Such a rapid onset of tezepelumab effects cannot be explained by only the suppression of IgE-mediated response via dendritic cells and CD4⁺ T cells in acquired immunity, implying that tezepelumab acts on other type of cells as well, such as ILC2s, mast cells, epithelial cells, airway smooth muscle, neurons, and fibroblasts.

Clinical trial of tezepelumab in Japanese patients with asthma

The NOZOMI study¹⁷ was conducted to evaluate the long-term safety of tezepelumab in Japanese patients with asthma. The NOZOMI study was a phase 3, open-label, single-arm study of 65 Japanese patients aged 12–80 years who had been diagnosed with asthma for at least one year and were using medium-to-high doses of inhaled corticosteroids and other asthma controllers. Tezepelumab 210 mg/dose was administered subcutaneously every 4 weeks for 52 weeks. Patients were followed up for 12 weeks after treatment to assess the frequency of adverse events which are the primary endpoints, as well as AAER and lung function. The results of the NOZOMI study showed that the incidence of adverse events was not different from that in the NAVIGATOR study,¹⁵ and no new adverse events were observed. On the other hand, AAER showed a remarkable suppression of 0.11/patient-year (mean number of exacerbations/patient in the last year: 1.3), but the prebronchodilator FEV₁ improved by only 75 mL, which was less than that observed in the NAVIGATOR study. It is possible that the patients enrolled in this study had better baseline pulmonary function (baseline FEV₁ (% FEV₁): 2.56 L (78.6%) in the NOZOMI study vs 1.8 L (62.8%) in the NAVIGATOR study); therefore, less improvement might have been

observed with tezepelumab treatment. Overall, the results of the NOZOMI study support the safety and efficacy of tezepelumab in Japanese patients with asthma.¹⁷

Studies investigating the mechanism of tezepelumab in asthma

Two studies have reported that bronchoscopy was performed before and after tezepelumab treatment to elucidate what changes caused by tezepelumab in the airways of patients with asthma.

The UPSTREAM study¹⁸ was a single-center, phase 2, randomized, double-blind, placebo-controlled study. In this study, 40 patients with poorly controlled asthma (ACQ-6 >1) and airway hyperresponsiveness induced by mannitol were randomly assigned to the tezepelumab and placebo groups. Tezepelumab 700 mg was administered intravenously every 4 weeks for 12 weeks, and then evaluated by airway hyperresponsiveness and bronchoscopy. In the tezepelumab group, the mannitol dose to reduce FEV₁ by 15% (PD₁₅), which was the primary endpoint, improved, but was not statistically significant ($p = 0.06$). However, mannitol did not induce airway hyperresponsiveness in nine patients in the tezepelumab group, which was significantly different compared to the three patients in the placebo group. There was also a marked decrease in eosinophil counts in the airway mucosa, BALF, sputum, and blood. This study analyzed mast cells as an important cause of airway hyperresponsiveness. Although there was a trend toward a slight decrease in the number of submucosal mast cells with tezepelumab treatment, the difference was not significant. Similarly, no changes were observed in the proportion of hematopoietic cells, including lymphocytes, neutrophils, and basophils in the blood and BALF following tezepelumab treatment. Therefore, this study could not elucidate a new mechanism for tezepelumab mode of action.¹⁸

The second study was the CASCADE study,¹⁹ a phase 2, multicenter, randomized, double-blind, placebo-controlled study. The study was designed to enroll 116 asthmatic patients receiving treatment with medium-to high-dose inhaled corticosteroids (≥ 250 μ g/day fluticasone equivalent) and one or more asthma controllers, who were to receive tezepelumab 210 mg/dose or placebo every 4 weeks subcutaneously for 28 weeks. However, due to the COVID-19 pandemic, the administration period was extended if the bronchoscopy could not be performed as scheduled. The number of eosinophils in bronchoscopy biopsy specimens after treatment, the primary endpoint, was significantly reduced (by 89%) in the tezepelumab group compared to 25% reduction in the placebo group. In addition, airway hyperresponsiveness induced by mannitol was significantly reduced in this study. However, no changes in the numbers of neutrophils, CD3⁺ T cells, CD4⁺ T cells, tryptase-positive mast cells, or chymase-positive mast cells were observed in the submucosa of the airways. The tezepelumab and placebo groups showed no differences in basement membrane thickness or airway epithelial fragility. Taken together, tezepelumab markedly suppressed eosinophils in the lungs, especially in the submucosa of the airways. However, other effects on neutrophils, mast cells, T cells, and epithelial cells were unclear. Therefore, the mechanism by which tezepelumab reduces AAER even in patients with low blood eosinophil counts, and the mechanism by which it rapidly improves airway hyperresponsiveness caused by both direct (methacholine) and indirect (mannitol) stimuli still remains unclear and requires further investigation.

Study evaluating the efficacy of tezepelumab in oral corticosteroid-dependent asthma

The SOURCE study^{20,21} was a phase 3, multicenter, randomized, double-blind, parallel-group, placebo-controlled trial evaluating

the efficacy of tezepelumab in patients with asthma who were taking oral corticosteroids. This study included 150 patients with severe asthma, who required maintenance therapy with oral corticosteroids (OCS) along with inhaled medium-to high-dose corticosteroids and long-acting beta2-stimulants, with a protocol of 36 weeks of OCS dose reduction phase. Under maintained asthma control, the rate of reduction in OCS dose was not significantly different between the tezepelumab and placebo groups. There was also no significant difference between the two groups when stratified by percentage decrease from baseline OCS dosage (90–100%, 75–90%, 50–75%, and 0–50%) at week 48. However, 54% of patients in the tezepelumab group (46% in the placebo group) discontinued OCS at week 48, and 74% of patients in the tezepelumab group (70% in the placebo group) could reduce their OCS dosage by 50% or more, with tezepelumab showing a favorable OCS reduction effect, although not significantly different from the placebo group. Furthermore, even under OCS reduction, tezepelumab reduced AAER at week 48 by 31% compared to placebo and improved prebronchodilator FEV₁ +260 mL versus the placebo. In addition, tezepelumab improved ACQ-6 levels and decreased blood eosinophil counts, FeNO levels, and serum total IgE levels. Sub-group analysis by blood eosinophil counts showed that patients with blood eosinophil counts of 150 cells/ μ L or higher showed a significant reduction in OCS dose after 48 weeks in the tezepelumab group, and other outcomes (AAER, FEV₁, and ACQ-6) also showed improvement compared to the placebo group. Therefore, it is a possibility that tezepelumab has a beneficial effect in patients with residual elevated eosinophils despite OCS treatment.

One of the reasons why the SOURCE study failed to achieve the primary endpoint despite the reduction in OCS in the tezepelumab group may be the high rate of OCS reduction in the placebo group. The OCS dose reduction protocol in the SOURCE study differed from other biologics' previous OCS dose reduction trials.^{22–24} In other OCS reduction trials, the OCS dose reduction phase was relatively short (16–20w), and the protocol did not permit further OCS dose

reduction if asthma was exacerbated or asthma control deteriorated. In contrast, the SOURCE study had a longer OCS reduction phase (36weeks) and allowed for subsequent OCS reductions even after exacerbations or worsening asthma control, leading to a higher rate of OCS reduction in the placebo group. Therefore, it may be necessary to modify the protocol and conduct the study again to assess whether the OCS reduction effects of tezepelumab are significant compared with the placebo group.

In contrast, in the PATHWAY and NAVIGATOR studies, tezepelumab showed efficacy regardless of blood eosinophil counts; however, in the SOURCE study, tezepelumab did not show any improvement in clinical outcomes in patients with low blood eosinophil counts. These results suggest that patients who are OCS-dependent and with low blood eosinophil counts may have different asthma pathophysiology compared to patients who do not receive OCS maintenance therapy and with low blood eosinophil counts. In other words, TSLP is not involved in the pathogenesis of asthma in patients with low blood eosinophil counts under OCS therapy. Therefore, further studies are needed to determine why the efficacy of tezepelumab in patients with low blood eosinophil counts differs with and without OCS.

Ongoing clinical trial of tezepelumab for asthma

The DESTINATION study²⁵ is a randomized, double-blind, placebo-controlled phase 3 extension study involving patients who had completed either the NAVIGATOR¹⁵ or SOURCE^{20,21} studies. The objective of this study was to evaluate long-term safety and efficacy for a total of 104 weeks, including the tezepelumab or placebo period from prior studies. The primary endpoint was adverse events over 104 weeks, and the secondary endpoint was AAER over 104 weeks. The interim analysis data showed no difference in overall adverse events, including cardiac disorders, but a numerical increase in serious cardiac disorders. As this study is ongoing, and

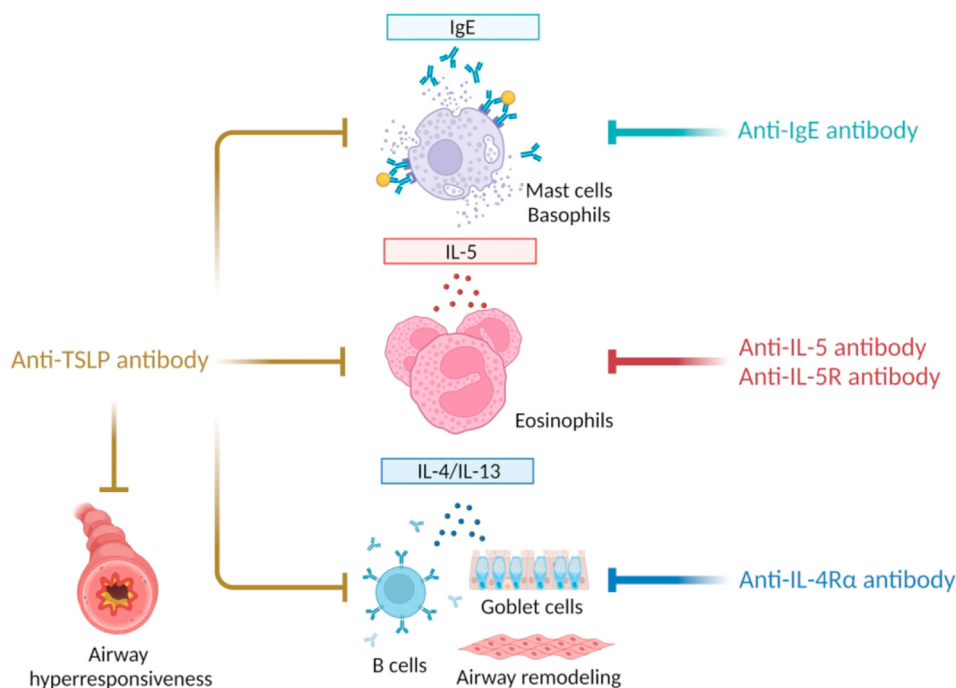


Fig. 1. Comparison of biologics for asthma. Anti-IgE antibody suppresses IgE-mediated activation of mast cells and basophils. Anti-IL-5 and IL-5 receptor (IL-5R) antibodies suppress eosinophil activation. Anti-IL-4Rz antibody suppresses B cell class switch, mucin production, and airway remodeling. Anti-TSLP antibody broadly suppresses all of these inflammation cascades, as well as airway hyperresponsiveness.

the final results are still awaited, it would be important to observe the outcomes in real-world practice.

Comparison of tezepelumab with other biologics for asthma

The most important feature of tezepelumab is its broad-spectrum inhibition of multiple cascades of type 2 inflammation. In contrast, previous biologics have been effective in specifically suppressing a single cytokine, cytokine receptor or IgE antibody. This new type of broad-target biologic may be less potent in suppressing a single cascade than previous specific-target biologics, but it suppresses the entirety of type 2 inflammation, as well as airway hyperresponsiveness (Fig. 1). Furthermore, tezepelumab suppresses asthma exacerbation in patients with poorly controlled, moderate-to-severe asthma, regardless of blood eosinophil counts, FeNO, or the presence of sensitization to perennial allergens. Menzies-Gow et al.²⁶ compared AAER with tezepelumab versus other biologics in two indirect treatment comparisons: a network meta-analysis and a simulated treatment comparison. The results showed that tezepelumab had a lower AAER than dupilumab, benralizumab, mepolizumab, reslizumab, and omalizumab, regardless of blood eosinophil counts or FeNO. Another network meta-analysis²⁷ also suggested that tezepelumab is an effective treatment option compared to other biologics, regardless of type 2 inflammation status. Therefore, tezepelumab may be considered as first-line biologic regardless of asthma phenotypes. However, the variation in baseline patient characteristics in each clinical trial is a limitation of these meta-analyses.

Previous biologics have had limited indications and responses, and no biologics have demonstrated inhibition of AAER in patients with low blood eosinophil counts (<150 cells/ μ L). Therefore, tezepelumab is the first drug expected to be effective on asthma exacerbation in patients with low eosinophil counts, although it has limited effects on pulmonary function, symptoms, and quality of life. Furthermore, other biologics, such as anti-IL-5R antibody and anti-IL-4R α antibody, have demonstrated efficacy in reducing OCS in OCS-dependent asthmatics, but tezepelumab failed to achieve its primary endpoint in the SOURCE study. Stratified analysis showed that patients with blood eosinophil counts of >150 cells/ μ L receiving OCS treatment showed significant OCS reduction and improvement of clinical outcomes by tezepelumab compared to the placebo group, whereas patients with low blood eosinophil counts (<150 or <300 cells/ μ L) receiving OCS treatment showed no improvement by tezepelumab. Therefore, these patients may be the only patient subgroup in whom TSLP is not involved in their asthma pathophysiology.

Conclusions

Tezepelumab is a biologic which targets an upstream cytokine in the pathogenesis of asthma and could become a broad-target biologic regardless of the asthma phenotype. However, the mechanism of efficacy in patients with non-type 2 phenotypes, the effect on OCS-dependent asthma, and long-term safety are still unclear and require further investigation.

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Conflict of interest

HK has received payment or honoraria for lectures from AstraZeneca, Sanofi, Novartis, GlaxoSmithKline, and Kyorin. KF has received grant funding from Boehringer Ingelheim, Ono Pharmaceutical, Chugai Pharmaceutical, and Taiho Pharmaceutical and has received payment or honoraria from Boehringer Ingelheim, Novartis, Sanofi, GlaxoSmithKline, and AstraZeneca.

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