VOLUME 11 ISSUE 2 2025

ISSN 2454 – 3055

INTERNATIONAL JOURNAL OF ZOOLOGICAL INVESTIGATIONS

Forum for Biological and Environmental Sciences

Published by Saran Publications, India

International Journal of Zoological Investigations Vol. 11, No. 2, 1048-1053 (2025)

International Journal of Zoological Investigations

Contents available at Journals Home Page: www.ijzi.net

Editor-in-Chief: Prof. Ajai Kumar Srivastav

Published by: Saran Publications, Gorakhpur, India

ISSN: 2454-3055

Tezepelumab: A New Era in Targeted Therapy for Severe Asthma

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Received: 26th March, 2025; **Accepted:** 22nd October, 2025; **Published online:** 5th December, 2025

https://doi.org/10.33745/ijzi.2025.v11i02.103

Abstract: Tezepelumab, marketed as Tezspire, is a human monoclonal antibody targeting thymic stromal lymphopoietin (TSLP), an epithelial cell-derived cytokine implicated in initiating and sustaining airway inflammation. Approved for use in individuals aged 12 and older with severe asthma, Tezspire offers a novel approach to asthma management by addressing upstream inflammatory pathways. TSLP plays a pivotal role in activating multiple downstream inflammatory mediators, including eosinophils, immunoglobulin E (IgE), and various interleukins, contributing to the pathophysiology of diverse asthma phenotypes. By inhibiting TSLP, tezepelumab may exert broad effects on these mediators, potentially benefiting patients irrespective of their specific asthma phenotype. The precise mechanism by which Tezspire ameliorates asthma symptoms is not fully elucidated. However, it is understood that by blocking TSLP, Tezspire disrupts the inflammatory cascade triggered by environmental stimuli, thereby reducing inflammation and preventing asthma exacerbations. This mechanism positions Tezspire as a proactive treatment option, targeting the underlying causes of inflammation rather than merely managing symptoms. Clinical studies have demonstrated that Tezspire effectively reduces asthma exacerbations and improves lung function across a broad patient population, regardless of baseline eosinophil counts or other type 2 inflammation biomarkers. At an end, Tezspire represents a significant advancement in the treatment of severe asthma by targeting TSLP, a key upstream regulator of airway inflammation. Its ability to reduce exacerbations and improve lung function across diverse patient populations underscores its potential as a versatile therapeutic option in asthma management.

Keywords: Asthma, Tezspire, Bronchial inflammation, Immunoglobulins, Lung function, Eosinophil

Citation: Sai Ramakrishna K., Hrushik Kowtinya R., Dinesh B., Eswar Tony D. and Siva Bharath G.: Tezepelumab: A new era in targeted therapy for severe asthma. Intern. J. Zool. Invest. 11(2): 1048-1053, 2025.

https://doi.org/10.33745/ijzi.2025.v11i02.103

Introduction

Asthma is a chronic respiratory condition characterized by airway inflammation, bronchial hyper-responsiveness, and intermittent airflow obstruction, affecting millions of individuals worldwide. According to the Global Initiative for Asthma (GINA), asthma affects over 300 million people worldwide, with approximately 10–20% of cases classified as severe asthma (Corren *et al*.,

2011). Despite the availability of various treatment options, including inhaled corticosteroids (ICS), long-acting beta-agonists (LABAs), leukotriene receptor antagonists, and biologics targeting interleukins, a significant proportion of patients with severe asthma remain inadequately controlled. This persistent burden has driven the development of novel therapies targeting upstream regulators of inflammation, offering a more comprehensive approach to disease management (Fahy *et al*., 2015).

One such advancement is Tezepelumab, marketed under the trade name Tezspire, a monoclonal antibody that represents a ground-breaking approach to asthma treatment by targeting thymic stromal lymphopoietin (TSLP), a cytokine involved in initiating and sustaining airway inflammation**.** Tezspire was developed through a collaboration between AstraZeneca and Amgen and was approved by the U.S. Food and Drug Administration (FDA) in December 2021 for the treatment of severe asthma in patients aged 12 years and older (Gauvreau *et al*., 2014). Unlike other biologics that target specific downstream inflammatory markers such as eosinophils or immunoglobulin E (IgE), Tezspire acts upstream by inhibiting TSLP, which is produced by epithelial cells in response to environmental stimuli, including allergens, viruses, and pollutants**.** By blocking TSLP, Tezspire prevents the activation of multiple downstream inflammatory pathways, providing a broad and comprehensive reduction in airway inflammation. TSLP is a key epithelial cytokine that plays a central role in the pathogenesis of asthma by activating dendritic cells, mast cells, eosinophils, and T-helper (Th2) cells, leading to the production of interleukins such as IL-4, IL-5, and IL-13. These interleukins contribute to eosinophilic inflammation, increased IgE synthesis, mucus hypersecretion, and airway remodeling. Traditional asthma therapies, including biologics like omalizumab (anti-IgE) and mepolizumab (anti-IL-5), target specific components of the inflammatory cascade. However, these therapies are primarily effective in patients with specific endotypes, such as eosinophilic or allergic asthma. Tezspire's ability to inhibit TSLP at the upstream level enables it to target a broader range of asthma phenotypes, including those driven by non-eosinophilic inflammation (Ziegler *et al*., 2010).

The clinical efficacy of Tezspire has been demonstrated in several key trials, including the PATHWAY and NAVIGATOR studies. In the PATHWAY study, Tezspire significantly reduced asthma exacerbations and improved lung function in patients with uncontrolled asthma, irrespective of baseline eosinophil counts. The NAVIGATOR trial further confirmed Tezspire's broad efficacy, showing a 56% reduction in exacerbations compared to placebo, with consistent benefits observed across patients with varying levels of type 2 inflammation biomarkers (Corren *et al*., 2017).

Importantly, Tezspire's mechanism of action allows it to address not only allergic and eosinophilic asthma but also non-type 2 asthma, making it a versatile treatment option**.** Another advantage of Tezspire is its favorable safety and tolerability profile. Clinical studies have reported minimal adverse effects, with the most common being injection site reactions, headaches, and nasopharyngitis. Unlike other biologics, Tezspire does not require biomarker-based patient selection, broadening its applicability to a wider patient population. The simplicity of its administration, with subcutaneous injections administered once every four weeks, enhances patient compliance and convenience (Menzies-Gow *et al*., 2021).

Pathophysiology of Asthma

Asthma is a chronic inflammatory disease of the airways characterized by airway hyper-responsiveness, mucus overproduction, bronchial constriction, and airway remodeling, leading to episodic symptoms such as wheezing, coughing, chest tightness, and shortness of breath (Al-Hajjaj *et al*., 2020). The pathophysiology of asthma (Fig. 1) is complex and involves a combination of genetic, environmental, and immunological

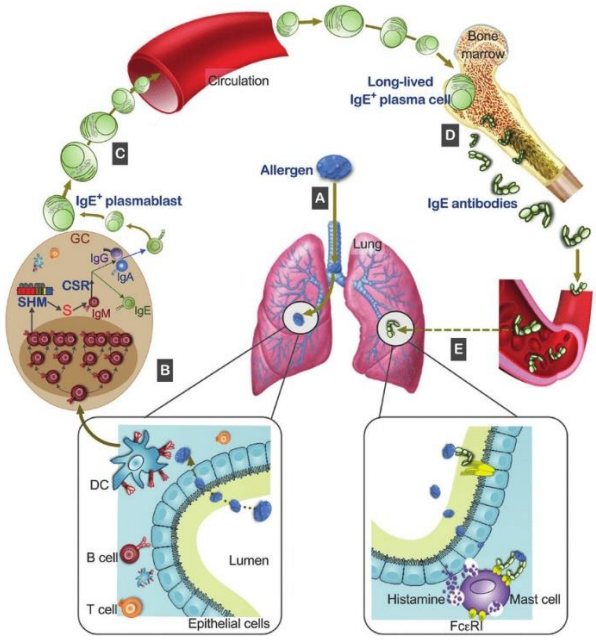

Fig. 1: Pathophysiology of Asthma (https://www.researchgate.net/figure/Compartmental-regulation-and-IgE-function-in-allergic-asthma-A-Allergen-is-inhaled_fig3_326671888).

factors. Environmental triggers such as allergens (e.g., dust mites, pollen, animal dander), respiratory infections (e.g., rhinovirus), irritants (e.g., tobacco smoke, air pollution), and physical factors (e.g., exercise, cold air) can activate the immune response and initiate airway inflammation (Wenzel *et al*., 2012). The epithelial cells lining the respiratory tract play a key role in initiating this inflammatory cascade. Upon exposure to environmental triggers, damaged epithelial cells release cytokines known as "alarmins," including thymic stromal lymphopoietin (TSLP), interleukin-25 (IL-25), and interleukin-33 (IL-33). These alarmins activate innate and adaptive immune cells, leading to the recruitment and activation of inflammatory cells such as dendritic cells, mast cells, eosinophils, and T-helper (Th) cells (Holgate *et al*., 2008).

TSLP is a key regulator in the pathogenesis of asthma as it triggers the activation of dendritic cells, which in turn promote the differentiation of naïve T cells into Th2 cells. Activated Th2 cells release type 2 cytokines such as interleukin-4 (IL-4), interleukin-5 (IL-5), and interleukin-13 (IL-13). IL-4 promotes the production of immunoglobulin E (IgE) by B cells, which sensitizes mast cells to allergens. Upon subsequent allergen exposure, IgE cross-linking on mast cells leads to the release of histamine, prostaglandins, and leukotrienes, which cause bronchoconstriction, increased vascular permeability, and mucus secretion (Brightling *et al*., 2016). IL-5 stimulates the recruitment and survival of eosinophils, which release cytotoxic granules and reactive oxygen species, leading to tissue damage and further airway inflammation. IL-13 promotes goblet cell hyperplasia, increased mucus production, and airway remodeling, contributing to airway obstruction and hyper-responsiveness (Gauvreau *et al*., 2020). Chronic inflammation also leads to structural changes in the airway, including subepithelial fibrosis (thickening of the basement membrane), smooth muscle hyper-trophy, and increased vascularity (angiogenesis), which collectively contribute to irreversible airflow limitation and airway hyperresponsive-ness (Brightling *et al*., 2016). While most asthma cases

are driven by type 2 (T2) inflammation involving Th2 cells and eosinophils, a subset of asthma cases is associated with non-type 2 (non-T2) inflammation, which is characterized by neutrophil infiltration and the involvement of Th1 and Th17 cells (Castro *et al*., 2018). In non-T2 asthma, Th1 cells release interferon-gamma (IFN-γ) and tumor necrosis factor-alpha (TNF-α), while Th17 cells release interleukin-17 (IL-17), which promotes neutrophilic inflammation (Humbert *et al.*, 2018) and tissue damage. Non-T2 asthma is less responsive to corticosteroids and traditional biologics, highlighting the need for novel therapies that target upstream inflammatory mediators involved in both T2 and non-T2 inflammation. TSLP serves as a common upstream regulator of both T2 and non-T2 inflammation, making it an attractive therapeutic target for broader asthma phenotypes (Humbert *et al*., 2018).

Mechanism of Action of Tezspire (*Tezepelumab*)

Tezspire (Tezepelumab) is a human monoclonal antibody that targets TSLP, a key cytokine involved in the initiation and maintenance of airway inflammation in asthma. Unlike existing biologics that target downstream cytokines such as IL-4, IL-5, and IL-13, Tezspire acts at the top of the inflammatory cascade by blocking TSLP's interaction with its receptor complex (Brusselle *et al*., 2022). TSLP binds to a heterodimeric receptor composed of the thymic stromal lymphopoietin receptor (TSLPR) and interleukin-7 receptor alpha (IL-7Rα) on the surface of immune cells (Menzies-Gow *et al*., 2022). Tezspire binds to TSLP with high affinity, preventing it from engaging with its receptor and thereby blocking the activation of downstream inflammatory pathways (Menzies-Gow *et al*., 2022). By inhibiting TSLP, Tezspire disrupts the recruitment and activation of dendritic cells, which are responsible for priming naïve T cells into Th2 cells. This prevents the subsequent release of type 2 cytokines (IL-4, IL-5, and IL-13) and reduces the downstream inflammatory response (Ziegler *et al*., 2022).

The inhibition of IL-4 production leads to a reduction in IgE levels and decreased mast cell sensitization, thereby reducing allergic responses and acute bronchoconstriction. By blocking IL-5 production, Tezspire reduces eosinophil recruitment and activation, leading to lower eosinophil counts in both the blood and airway tissue. Inhibition of IL-13 reduces mucus hypersecretion, goblet cell hyperplasia, and smooth muscle hypertrophy, resulting in improved airway function and reduced airway hyperresponsiveness. Tezspire's broad mechanism of action allows it to address both eosinophilic and non-eosinophilic asthma phenotypes, making it effective in patients who are not responsive to existing type 2-targeted biologics (Lin *et al*., 2023).

Tezspire's efficacy has been demonstrated in several key clinical trials, including the PATHWAY and NAVIGATOR trials. In the PATHWAY study, Tezspire significantly reduced asthma exacerbations by 61% compared to placebo in patients with moderate to severe asthma. Importantly, the reduction in exacerbations was observed regardless of baseline eosinophil counts, demonstrating Tezspire's efficacy in both type 2 and non-type 2 asthma. The NAVIGATOR trial further confirmed Tezspire's broad efficacy, showing a 56% reduction in exacerbations and improved lung function across a wide range of patient populations. In both trials, Tezspire also improved patient-reported asthma control and quality of life (Menzies-Gow *et al*., 2022).

Tezspire has a favorable safety and tolerability profile. The most commonly reported adverse effects include injection site reactions, nasopharyngitis, and headaches, which were mild to moderate in severity. Importantly, Tezspire does not require biomarker-based patient selection, unlike other biologics that target specific type 2 inflammatory pathways. This broad eligibility makes Tezspire a valuable treatment option for patients with severe asthma who have previously failed other therapies. Tezspire is administered as a once-monthly subcutaneous injection, which improves patient compliance and convenience compared to therapies requiring

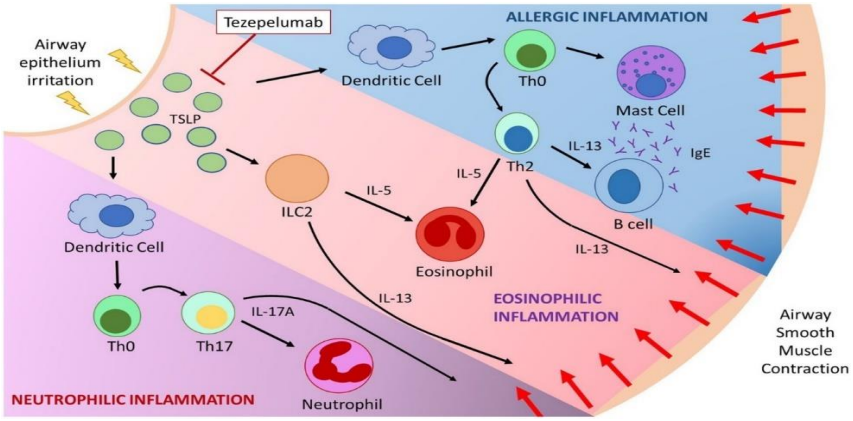

Fig. 2: Mechanism of Action of Tezepelumab.

(https://journals.sagepub.com/doi/full/10.1177/10600280221095540).

Table 1: Comparison between Existing Therapies and Tezepelumab

Drug	Target	Patient Population	Frequency	Efficacy
Omalizumab	IgE	Allergic asthma	Every 2-4 weeks	Moderate
Mepolizumab	IL-5	Eosinophilic asthma	Every 4 weeks	Moderate
Dupilumab	IL-4, IL-13	Type 2 asthma	Every 2 weeks	Moderate to high
Tezspire	TSLP	Broad asthma phenotypes	Every 4 weeks	High

more frequent administration (Kaur *et al*., 2023).

The unique mechanism of action of Tezspire (Fig. 2) distinguishes it from other biologics currently used for asthma treatment. For instance, omalizumab targets IgE and is only effective in allergic asthma, while mepolizumab and reslizumab target IL-5 and are specifically used in eosinophilic asthma. Dupilumab targets IL-4 and IL-13, making it effective only in type 2 inflammation (Table 1). In contrast, Tezspire's upstream targeting of TSLP allows it to modulate both T2 and non-T2 inflammatory pathways, making it effective in a broader range of asthma phenotypes. Tezspire's broad efficacy, convenient dosing schedule, and favorable safety profile position it as a promising first-line biologic for patients with severe, uncontrolled asthma (Brightling *et al*., 2024).

Future Directions

- Further investigation into Tezspire's long-term safety and efficacy.
- Evaluation of its potential benefits in other airway diseases (e.g., chronic obstructive pulmonary disease).
- Combination strategies with other biologics for enhanced outcomes in refractory asthma cases.

Conclusion

Tezspire represents a paradigm shift in asthma treatment by addressing the root cause of airway inflammation at the top of the inflammatory cascade. Its ability to target both type 2 and non-type 2 inflammation sets it apart from existing therapies, providing hope for patients with severe asthma who have not responded to conventional treatments. The demonstrated clinical benefits, combined with its ease of administration and broad patient applicability, make Tezspire a valuable addition to the therapeutic landscape for asthma management.

Ethical Statement

No animal or microbes have been used or sacrificed for this study, hence Ethical Approval

not required.

Author Contributions

Each author has contributed equally to the study's planning, analysis, writing, and editing. All authors have read and agreed to the published version of the manuscript.

Conflict of Interest

The authors declare no conflicts of interest.

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