REVIEW

Role of Thymic Stromal Lymphopoietin in the Pathophysiology of Asthma and Clinical and Biological Effects of Blockade With Tezepelumab

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Abstract

The airway epithelium is the first line of defense of the respiratory system against the external environment. It plays an active role in the initiation of immune and allergic responses against potential hazards. Among the various specialized cells and cytokines that participate in epithelium-induced responses, alarmins are particularly interesting, given their ample role in mediating T2 and non-T2 inflammatory mechanisms involved in the pathogenesis of asthma. Thymic stromal lymphopoietin (TSLP) is an alarmin with broad effects in asthma that result from its widespread action on multiple cell types, including eosinophils, mast cells, dendritic cells, and group-2 innate lymphoid cells. Its role in allergy-mediated responses, eosinophilic inflammation, airway hyperresponsiveness, mucus hyperproduction, viral tolerance, and airway remodeling is of the utmost importance, as more comprehensive asthma assessments have been developed to explore these pathogenic features. Therefore, blockade with targeting molecules, such as monoclonal antibodies, has emerged as a promising therapeutic option, particularly in patients with multiple pathogenic pathways. In this review, we examine the roles of alarmins (mainly TSLP) in the pathogenesis of asthma and clinical expression and discuss the effects of inhibiting TSLP on several inflammatory and clinical outcomes. We also review the literature supporting treatment with anti-TSLP biologics and the unanswered questions and unmet needs associated with targeting alarmins in asthma.

Key words: Severe asthma. Airway epithelium. Alarmins. TSLP. Tezepelumab. Biologicals.

Resumen

El epitelio de las vías respiratorias representa la principal línea de defensa del aparato respiratorio al estar en contacto con el medio externo y desempeña un papel activo en la incepción de las respuestas inmunitarias y alérgicas ante posibles amenazas. Entre las diversas células y citocinas especializadas que participan en las respuestas epiteliales, las alarminas han despertado un interés particular, debido a su importante participación en el desarrollo de los mecanismos inflamatorios T2 y no T2 implicados en la patogenia del asma. La TSLP es una alarmina que ejerce amplios efectos en el asma, derivados de su actuación sobre múltiples tipos celulares, entre las que se encuentran los eosinófilos, los mastocitos, las células dendríticas y las células linfoides innatas de tipo 2. Su actuación en las respuestas alérgicas, la inflamación eosinofílica, la hiperrespuesta de las vías respiratorias, la hiperproducción de moco, la tolerancia viral y la remodelación de las vías respiratorias es de suma importancia, puesta de relieve a medida que se han ido desarrollado evaluaciones más exhaustivas sobre estos efectos patogénicos. Por ello, su bloqueo con moléculas selectivas como los anticuerpos monoclonales se ha convertido en una opción terapéutica prometedora, especialmente en pacientes con múltiples vías patogénicas implicadas. En esta revisión, se examina el papel de las alarminas (particularmente la TSLP) en la patogenia y las manifestaciones clínicas del asma y se comentan los efectos de la inhibición de TSLP sobre distintos aspectos inflamatorios y clínicos. También se revisa la bibliografía actualmente disponible relativa al tratamiento con anticuerpos anti-TSL, así como preguntas aún no respondidas y necesidades insatisfechas relativas al papel de las alarminas en el asma.

Palabras clave: Asma grave. Epitelio de las vías respiratorias. Alarminas. TSLP. Tezepelumab. Biológicos.

Introduction: The Epithelium and the Initiation of the Immune Response in Asthma

Epithelial barriers are the frontline defense against threats and harmful agents from the external environment. Their role goes beyond that of mere physical barriers, with their participation in the initiation of the immune response [1]. They are now recognized as dynamic immune interfaces with a complex structure of highly specialized cells that respond to microorganisms and noxious agents and interact with the resident microbiota and the immune and neuroendocrine systems [2] to provide the appropriate response to a wide variety of environmental insults.

Epithelial barrier cells can induce a type-2 (T2) response to various stimuli, such as large multicellular organisms (nematodes), tick proteins, venoms, mite and cockroach molecules, molds, bacterial cell wall components, enzymes, animal dander, plant pollen, and even inorganic substances. This activation can occur through protease-activated receptors, Toll-like receptors, C-type lectin receptors, and inflammasomes, all of which sense invasion and penetration [3]. In the respiratory system, this complex cross-talk between environmental stimuli and the epithelial cell layer promotes the release of a plethora of molecules, including chemokines, cytokines, antimicrobial peptides, and extracellular matrix components. Among these, the release of alarmins and activation of their specific receptors play a crucial role in the initiation of T2 and, to a lesser extent, non-T2 responses in asthma [4].

Alarmins, including thymic stromal lymphopoietin (TSLP), interleukin (IL) 33, and IL-25, act at the beginning of the inflammatory cascade and can trigger both acquired and innate responses by activating innate immune cells, adaptive immune cells, and structural cells, thus contributing to T2 and non-T2 asthma mechanisms. In T2 asthma, the activation of the adaptive or innate immune response can lead to allergic inflammation (frequently with eosinophilia) or eosinophilic nonallergic inflammation [5]. In allergic asthma, activated dendritic cells can migrate to lymph nodes, present the antigen to T-naïve cells, and induce the production of T2 cytokines such as IL-4, lL-13, and IL-5. IL-4, also released by mast cells and basophils, mediates IgE switching; IL-5 is essential for the development, proliferation, survival, and activation of eosinophils; and IL-13 can increase barrier permeability, facilitate the migration of eosinophils to peripheral tissues, and induce mucus production [6]. In eosinophilic nonallergic asthma, the release of epithelial alarmins activates downstream

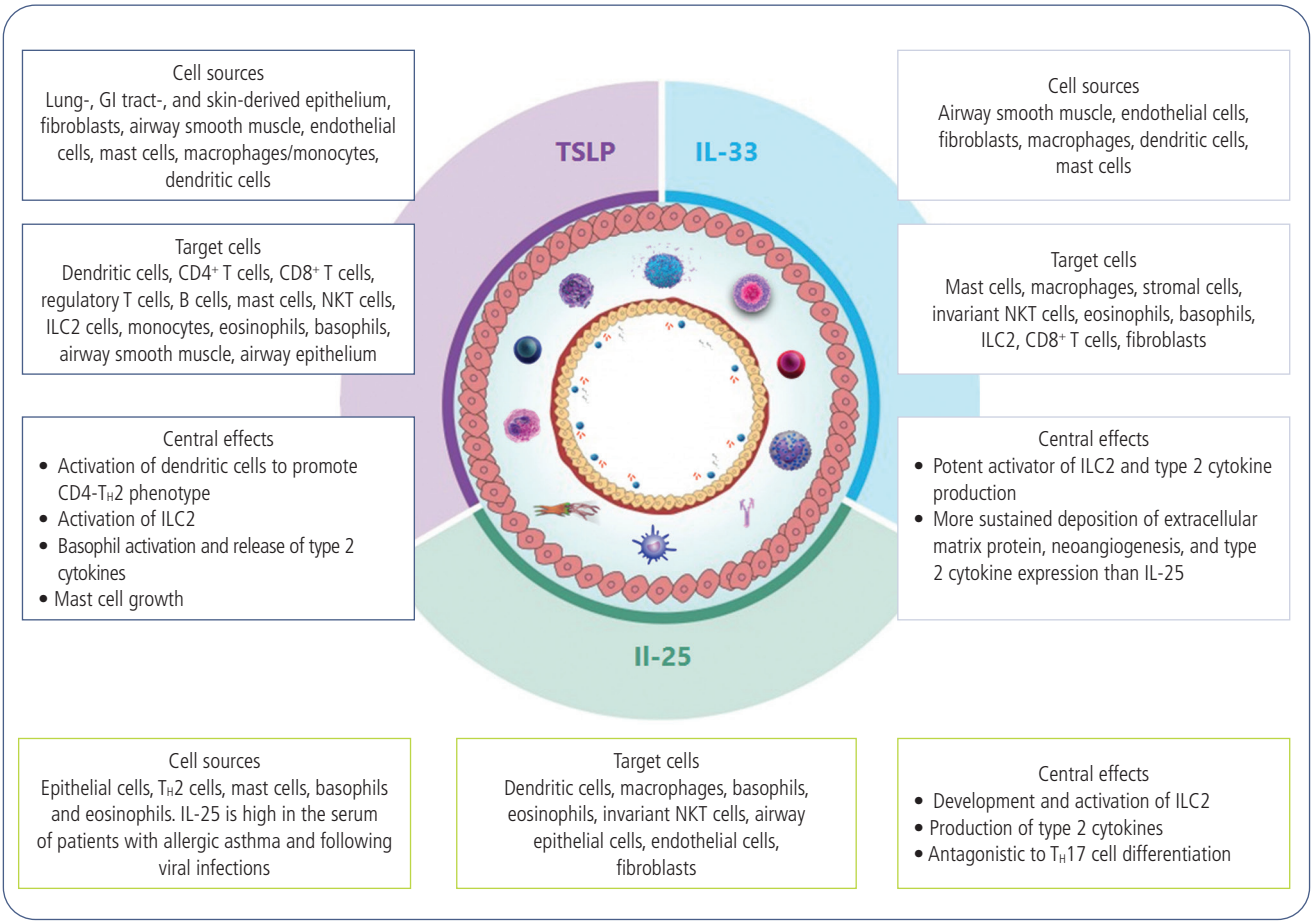

Figure 1. Thymic stromal lymphopoietin (TSLP), interleukin (IL) 33, and IL-25 are considered alarmins, which are released by the epithelia and participate in the inception of immune reactions. Cell sources, target cells, and main effects are shown for each. GI indicates gastrointestinal; T_H, helper T cell; ILC2, type-2 innate lymphoid cell; NKT, natural killer T cell.

type-2 innate lymphoid cells (ILC2) to produce significant amounts of IL-5 and IL-13 [7,8]. Finally, neutrophils, T_H1 and T_H17 cells, interleukins (IL-1, IL-6, and IL-8), airway smooth muscle, and neurogenic mechanisms have been involved in non-T2 asthma (encompassing neutrophilic and paucigranulocytic asthma) [7,9].

The objectives of this review are to describe the contribution of alarmins (particularly TSLP) to the pathogenesis and severity of asthma and to assess the effect of alarmin blockade in T2 and non-T2 severe asthma features such as eosinophilic inflammation, airway hyperresponsiveness (AHR), and mucus plugging. We also examine the existing evidence regarding the use of an anti-TLSP antagonist, tezepelumab, for treating patients with severe asthma and explore the remaining uncertainties faced when using this biologic in this specific population.

Alarmins and Asthma: From Biology to Clinical Expression

The role of alarmins in the pathogenesis of chronic respiratory diseases has been extensively described, particularly in asthma and COPD. The release of TSLP, IL-25, and IL-33 by epithelial cells in response to allergens, pollutants, viruses, and local cytokines promotes several inflammatory responses, leading to diverse pathogenic phenomena that ultimately manifest as specific clinical features [10-12].

In asthma, expression of alarmins is amplified through increased production from the airway epithelium and activation of specific receptors in dendritic cells, ILC2, mast cells, basophils, macrophages, and NK cells [13-16]. A complex interaction between the inflammatory insult, the airway cellular microenvironment, and genetic polymorphisms of alarmins and their receptors modulates T_H1 and T_H2 cell differentiation and specific inflammatory signatures [15,17,18], which in turn result in T2 and non-T2 inflammatory cascades [19,20]. Figure 1 illustrates the sources and target cells of alarmins and their main immune and inflammatory effects.

TSLP Biology in Asthma and Its Role in the Pathogenesis of Asthma

TSLP is an alarmin that is also classified as a type I cytokine closely related to IL-7 [21]. In humans, its gene is located on chromosome 5q22.1, in a region that encodes other genes involved in allergic cytokines [12]. It is secreted in 2 forms depending on the signaling that activates the nucleus: the short form (present in skin, salivary glands, oral mucosa, and intestine) participates in homeostasis, while the long form (expressed in the lung) has a predominantly inflammatory role [4]. As with other alarmins, TSLP is released by epithelial cells and cells such as the stromal cells in mucosal barriers, although it can also be secreted by dendritic cells, basophils, and mast cells upon various intraluminal stimuli. It binds to a heterodimeric receptor of TSLP (TSLPR) and the IL-7 receptor

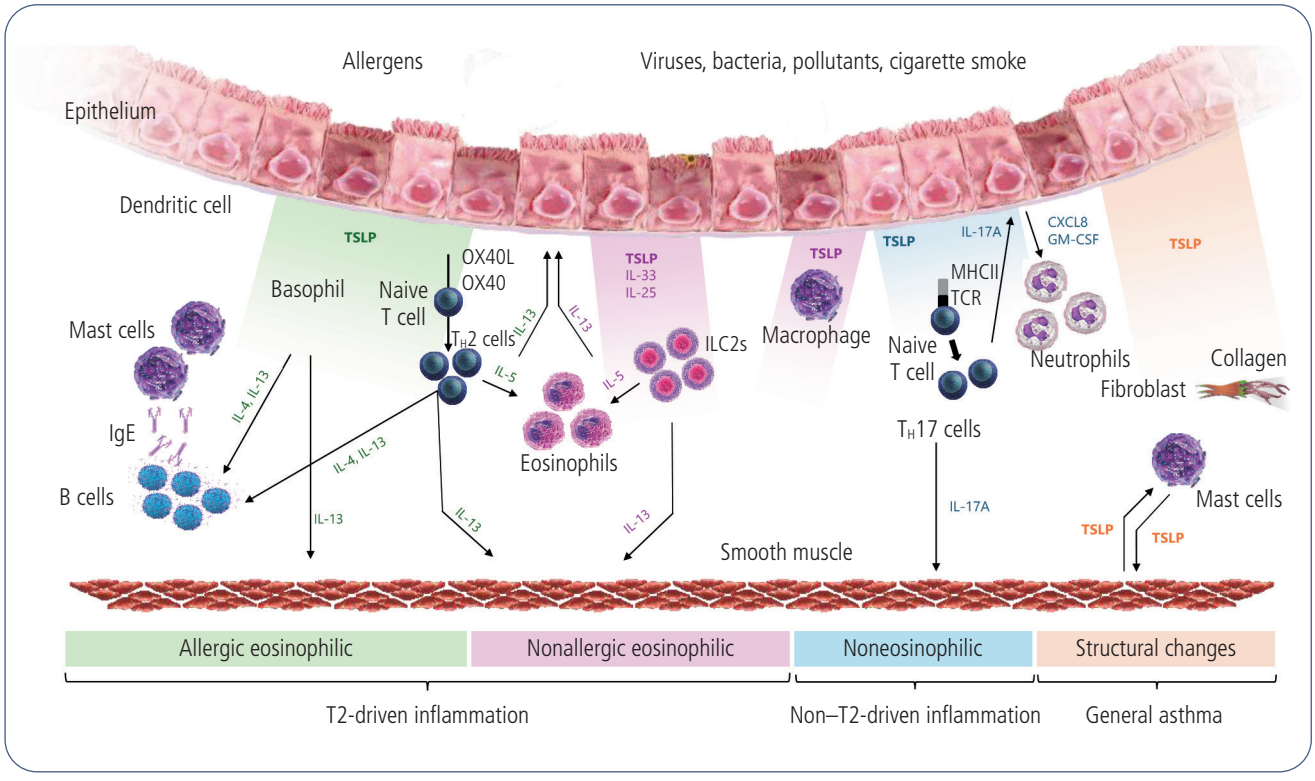

Figure 2. In asthma, the epithelium responds to various noxious agents, such as allergens, viruses, bacteria, pollutants, and cigarette smoke. Upon activation, epithelial cells release alarmins, ie, thymic stromal lymphopoietin (TSLP), interleukin (IL) 33, and IL-25, which participate in a very early stage of the inflammatory cascade. TSLP participates in the development of T2 asthma (allergic asthma and eosinophilic nonallergic asthma) and non-T2 asthma. TH indicates helper T cell; ILC2, type-2 innate lymphoid cell; MHC, major histocompatibility complex; TCR, T-cell receptor; TSLP, thymic stromal lymphopoietin.

α-chain (IL-7Rα or CD127) [22,23] and activates JAK1 (via IL-7Rα) and JAK2 (via TSLPR) [24].

TSLP has a particularly relevant role in asthma, illustrated by the increased risk of developing the disease in carriers of specific TSLP genetic variants [25-28]. Similarly, individuals with asthma are characterized by higher expression of TSLP and its derived cytokines in the bronchial mucosa and bronchoalveolar lavage (BAL) fluid than controls [19-29]. TSLP has been shown to increase eosinophil counts in the blood and airway mucosa of persons with asthma as a result of IL-5 and IL-13 production from mast cells, $CD34^+$, and ILC2 [30,31] and to indirectly promote IgE release through downstream effects on B cells [24]. In addition, TSLP induces mast cell proliferation and differentiation from bone marrow progenitors and stimulates the degranulation of preformed mediators and production of prostaglandins and leukotrienes [31,32], further enhancing T2 responses through redundant inflammatory mechanisms. This raises the possibility that prostaglandins and leukotrienes might mediate most of the clinically relevant effects of TSLP in asthma.

While the spectrum of action of TSLP has traditionally been linked to T2 processes, emerging evidence has shown that non-T2 mechanisms could also be promoted by this alarmin, including T_H17 differentiation, neutrophilic inflammation, and airway remodeling [33,34]. Given the pleiotropic effects of TSLP in the asthma inflammatory cascade, its expression has been correlated with multiple pathological features observed in asthma, including blood and airway eosinophilia, AHR, and goblet cell hyperplasia with mucus hyperproduction [35,36]. Moreover, TSLP levels in the airway mucosa have been associated with worsening airflow obstruction and disease severity [19,29,37], regardless of eosinophil levels [38], and previous studies suggested that its effect on the human airway small muscle could promote remodeling changes facilitated by mast cell activation [39,40]. The broad effects of TSLP and its complex interaction with multiple other cytokines and immune and airway structural cells are illustrated in Figure 2.

Modulatory Effects of TSLP Blockade on the Pathophysiology of Severe Asthma

Targeting TSLP has emerged as a very promising therapeutic strategy in asthma. Initial evidence on the effect of inhibiting TSLP showed reduced lung inflammation in terms of eosinophil counts and IL-5 and IL-13 levels in the BAL fluid of monkeys treated with a humanized anti-TSLPR monoclonal antibody (mAb) [41]. These results have been replicated in other animal models and associated with a reduced response to allergen challenge [42]. Interestingly, the findings were not correlated with a rebound of T1-driven inflammation [41].

Likewise, direct TSLP blockade using an intravenous human mAb to inhibit the interaction with its receptor was demonstrated to reduce inflammatory markers such as blood and airway eosinophilia and exhaled nitric oxide (FeNO), as well as allergen-induced bronchoconstriction [43]. More recently, a fully human IgG1 mAb against the TSLPR has been shown to inhibit $CD4^+$ T-cell differentiation and IL-5 production in in vitro models, and preliminary clinical data from a phase 1b trial demonstrated reduced maximal FeNO levels in adults with asthma and elevated blood eosinophils (ClinicalTrials.gov NCT05448651).

The effects of TSLP blockade on distinctive features of asthma are summarized below.

Eosinophil Depletion

Early clinical studies showed that blood and airway eosinophil counts were reduced after 2 and 6 weeks of a single IV dose of a fully human IgG2λ TSLP antagonist, tezepelumab [43]. Reduction in baseline eosinophils suggested that TSLP was constitutively activated, even in the resting state. Furthermore, the increase in eosinophil count following an allergen challenge was significantly lower in the treatment group in both blood and sputum [43]. These initial observations were later validated in clinical trials that assessed the efficacy of subcutaneous tezepelumab 210 mg in asthma inflammatory markers. The dose-finding phase 2b PATHWAY study and its post hoc analyses corroborated a significant decrease in blood eosinophils independently of atopic status or the presence of nasal polyposis [44-46], with a persistent effect observed throughout 52 weeks of treatment in the pivotal phase 3 NAVIGATOR study [47]. The effect of tezepelumab on local eosinophilic inflammation was explored in the CASCADE study, which showed a nominally significant reduction in airway submucosal eosinophils independently of baseline blood eosinophils [48], and in the UPSTREAM study, which showed a 74% reduction in airway tissue eosinophils and a 75% reduction in BAL eosinophils [49]. It should be recognized, however, that the UPSTREAM study involved 700 mg IV and not 210 mg SC. A similar effect was observed in a recently published phase 1 randomized clinical trial examining an inhaled anti-TSLP mAb fragment in mildly atopic asthma patients; however, no changes were seen in the blood eosinophil counts [50]. Interestingly, while the corticosteroid-sparing SOURCE study showed a comparable effect on eosinophil reduction in prednisone-dependent severe asthma, this change was not correlated with a parallel reduction in oral corticosteroid doses [51].

Airway Hyperresponsiveness

In an elegant proof-of-concept study, Gauvreau et al [43] demonstrated that TSLP blockade (with 700 mg IV) can increase methacholine PC20 following allergen challenge in adults with mild asthma and baseline T2 airway inflammation. These observations are supported by subsequent randomized clinical trials showing attenuated AHR to mannitol in patients with moderate-to-severe asthma treated with tezepelumab compared to placebo. Although this was not the primary endpoint, the CASCADE study showed that patients who received tezepelumab 210 mg SC had a nominally significantly greater reduction in AHR to mannitol, as well as a numerically greater proportion of negative mannitol responders than the placebo group, even if this was not the main objective of the study [48]. Similarly, the UPSTREAM study showed a greater mean change in PD15 at 12 weeks of treatment with tezepelumab 700 mg IV compared with individuals receiving placebo; however, this difference was not statistically

significant and became attenuated by week 21 of treatment. The authors also reported a statistically significant decrease in the percentage of patients with negative mannitol test results at the end of the trial [49]. Despite a larger effect observed in patients with eosinophilic asthma, the absence of a similar improvement in AHR with the currently available anti–IL-5 biologics compared to placebo (outside a small proof-of-concept study, where PD10 was used as a primary outcome instead of the more widely accepted PD15 [52]) suggests that this outcome might be eosinophil-independent.

Mast Cell Signatures

Despite the well-recognized effect of TSLP on mast cell biology and activation, particularly in severe, uncontrolled asthma [40,49,53], clinical trials with tezepelumab have failed to demonstrate a reduction in mast cell numbers or in their mediators [48]. However, indirect evidence of mast cell suppression could be inferred from the abolition of otherwise classical mast cell-mediated phenomena [43,48,49].

Mucus Hypersecretion

Intraluminal mucus is an increasingly recognized asthma feature with a relevant role in airway obstruction that is associated with multiple adverse clinical outcomes [54]. Given the strong correlation between mucus hyperproduction and T2-driven mechanisms (particularly IL-13 activity) [55], broader T2 suppression through TSLP blockade is an attractive therapeutic option for reducing mucus plugging. In this setting, a subsequent analysis of the CASCADE trial cohort revealed a statistically significant—albeit not necessarily clinically relevant—difference in mucus plugging quantified as a mucus score after 28 weeks of treatment with tezepelumab [56]. The impact of this biologic on mucus plugging and its functional relevance measured using lung MRI is being examined in an ongoing placebo-controlled RCT of tezepelumab in patients with moderate-to-severe asthma (ClinicalTrials.gov NCT05280418).

Clinical Responses to Tezepelumab

Tezepelumab is the only TSLP-targeting biologic currently approved for treatment of asthma. Its most compelling clinical effect is the reduction in asthma exacerbations in adults with severe, uncontrolled asthma, with greater efficacy observed among individuals with higher blood eosinophil counts and/or elevated FeNO [44,47,57]. Additional clinical outcomes, such as improvement in FEV_1 and control of asthma symptoms, have been observed with tezepelumab [58]. Significant improvements in symptoms and lung function were observed as soon as 8 weeks [59], and the effect on reducing exacerbations was maintained throughout the 104 weeks of the DESTINATION study [60]. Post hoc analyses of randomized controlled trials have demonstrated the efficacy of tezepelumab in patients regardless of sex [61], severe allergic asthma phenotype (patients with a history of allergy and confirmed sensitization to dust mite or animal allergen) [62], age of onset [63], smoking habit (former or nonsmokers) [64], nasal polyposis [65], or body mass index [66].

However, no convincing corticosteroid-sparing effect was demonstrated in the only study published to date evaluating this outcome in patients with severe asthma (SOURCE) [51]. This study did not meet the primary endpoint of corticosteroid dose reduction at week 48 of treatment with tezepelumab, although when participants were grouped by blood eosinophil count (no minimum level was required at baseline), greater reductions in OCS use were recorded in individuals with blood eosinophil counts of >150/μL. Along these lines, an early-trend analysis of an ongoing, open-label, single-arm, OCS-sparing study (WAYFINDER) showed a benefit in achieving protocol-driven reductions in the maintenance OCS dose while maintaining asthma control [67]. A subanalysis of the DESTINATION extension study concluded that a numerically higher proportion of tezepelumab recipients than placebo recipients discontinued OCS over 104 weeks without losing control of asthma [68]. This controversy is expected to be resolved with the information provided by the multicenter, double-blind, placebo-controlled, parallel-group SUNRISE study [69] on asthma patients with a blood eosinophil count of ≥150/μL or a documented blood eosinophil count of ≥300/μL within the 12 months before study entry.

Given the role of TSLP as an upstream messenger between airway structural cells and immune cells in response to stimuli, its blockade could be anticipated to be particularly effective in major clinical outcomes such as asthma remission. Data from large national and international registries of biologic-treated asthma patients had previously shown that only 18%-27% achieve clinical remission (defined as the cessation of exacerbations and maintenance OCS, as well as normalization of lung function [FEV_1% >80%] and control of symptoms) [70-74]. Similar results have been observed with tezepelumab, as shown in a post hoc analysis of the NAVIGATOR study, where only 53 out of 417 patients (12.7%) met this endpoint [75]. With a less rigorous definition of the outcome remission (Asthma Control Questionnaire-6 score ≤1.5, stable lung function [FEV_1 >95% of baseline] at the end of each year, and no exacerbations or use of OCS during the assessment period), a more compelling 27% of the patients included in the DESTINATION study were able to achieve clinical remission [76].

In terms of T2 biomarkers, tezepelumab has been shown to reduce FeNO levels [43,44,48] and serum IgE levels [43,44,47]. A similar T2-suppressing response was observed in a subanalysis of the NAVIGATOR trial, where, at week 52, approximately 80% of patients treated with tezepelumab achieved a blood eosinophil count <300/μL and FeNO <50 ppb and approximately 40% of patients treated with tezepelumab achieved a blood eosinophil count <150/μL and FeNO <25 ppb [77]. However, these overall broad findings have not yet provided the complete picture that may help clinicians predict response to treatment in different asthma endotypes. As such, further analysis and long-term follow-up of previously studied cohorts should provide the necessary evidence to determine the optimal clinical scenario for antialarmin treatment.

Discontinuation of tezepelumab after 2 years of treatment correlated with a progressive decline in asthma control and lung function over a 40-week follow-up period. Additionally, a steady increase in biomarker levels such as blood eosinophil

counts and FeNO was seen, although not reverting to the baseline levels; interestingly, 22% of tezepelumab recipients who continued into the 36-week extended follow-up remained in remission after the last dose [78].

To date, no data on asthma exacerbations, improvement in FEV_1, or other clinical outcomes have been published for inhaled anti-TSLP mAbs, despite at least 1 clinical trial on 336 patients with severe asthma being completed in 2022 (ClinicalTrials.gov NCT04410523).

Uncertainties and Therapeutic Limitations When Targeting TSLP in Asthma

While the pivotal trials of tezepelumab achieved the expected endpoints of reducing the rate of asthma exacerbations and improving pulmonary function [44,47,60], several questions remain to be answered regarding treatment with this anti-TSLP biologic.

The appropriate dose of tezepelumab is perhaps the main unresolved issue when it comes to addressing specific features of asthma. The currently approved dose of 210 mg SC every 4 weeks has demonstrated effects on the above-mentioned outcomes, as well as on patient-reported outcomes, FeNO levels, and blood and airway submucosal eosinophils; however, no convincing improvement in AHR has been published on this regimen to date, with only 1 published clinical trial reporting a nominally significant reduction in AHR to mannitol. Furthermore, the strongest evidence supporting the effectiveness of tezepelumab in AHR comes from studies using 700 mg IV on a smaller number of patients [43,49]. To date, tezepelumab is the only biologic that has demonstrated an improvement in AHR. However, this effect seems modest (0.9 doubling dose improvement in PC15 mannitol) and likely not clinically relevant. As such, further studies based on 210 mg should be conducted to confirm the role of tezepelumab in AHR.

Also uncertain is the effectiveness of tezepelumab in eosinophilic inflammation. While lower eosinophil blood counts were observed among the treatment groups in the PATHWAY, NAVIGATOR, and CASCADE trials, a similar effect in airway and tissue eosinophils remains less clear. Again, the most compelling evidence for tezepelumab reducing local eosinophilia is found in the results for 700 mg IV, with a mechanistic study demonstrating a reduction in sputum eosinophils following allergen challenge and a clinical trial with 20 patients per arm where patients in the active drug group had less airway tissue and a lower eosinophil count in BAL fluid [49]. Furthermore, the failure to achieve the OCS-sparing outcome despite a significant reduction in blood eosinophil counts in the SOURCE study may suggest an inadequate local effect, similar to observations for lower doses of anti–IL-5 biologics [79-81].

While the modulation of T2 and non-T2 responses by TSLP suggests a potential role of tezepelumab in noneosinophilic/nonatopic asthma [10], the literature has not provided convincing evidence supporting the effectiveness of anti-TSLP biologics outside T2-high endotypes, and the most significant effect of tezepelumab in reducing the annualized asthma exacerbation rate (AAER) was observed in patients with higher eosinophil counts. In the PATHWAY and NAVIGATOR studies, the reduction in AAER was significant independently of T2 status; however, the definition of T2-low was based merely on the criteria of <140 eosinophils/μL and IgE level <100 IU/mL in PATHWAY and <300/μL in NAVIGATOR. Furthermore, the results of the pooled analysis of the PATHWAY and NAVIGATOR clinical trials showed that while tezepelumab reduced exacerbations in patients with <150/μL and FeNO <25 ppb, this reduction was not statistically significant [66]. As previously described, this T2-low definition based on blood eosinophil count and FeNO values might be largely imprecise, considering that a single timepoint measurement tends to be misleading [82].

A meta-analysis summarizing the results of 6 RCTs assessing antialarmin therapy on clinical outcomes and asthma biomarkers revealed that while there is a statistically significant reduction in asthma exacerbations, this effect was less pronounced in individuals with low blood eosinophil counts [83]. A greater discrepancy was found in the effect on FEV_1 when the groups were compared (high vs low eosinophil counts), as treatment with antialarmins was unlikely to improve FEV_1 in this population. In this setting, further studies with a more comprehensive assessment of baseline inflammatory status need to be conducted to examine the effect of alarmin-targeting therapies in true low-T2 asthma patients.

Additionally, tezepelumab reduces inflammatory mediators but not consistently or to the same extent in all patients. As mentioned above, the CASCADE trial showed that tezepelumab resulted in a nominally significant reduction in airway submucosal eosinophils in bronchial biopsies accompanied by a significant decrease in T2 biomarkers, including blood eosinophils, serum T2 cytokines (IL-5, IL-13, total IgE, and eosinophil-derived neurotoxin), and FeNO [48]. However, these results should be interpreted with caution. Firstly, most of the assessments were performed in blood and not in the airways, potentially painting an inaccurate picture of the local pathophysiological process in severe asthma [84,85]. Secondly, while there is an observed reduction in T2 inflammatory biomarkers, no uniform effect among patients was demonstrated, and normalized levels were not consistently achieved. In this setting, a post hoc analysis of the NAVIGATOR trial revealed that 56% and 63% of the tezepelumab-treated patients achieved <150/μL and FeNO <25 ppb, respectively [77]. Therefore, it could be speculated that the inflammatory effect might be insufficient or not clinically relevant in some patients, although this aspect should be specifically investigated.

The relevance of redundant immunological mechanisms must be considered when assessing the effects of blocking a single alarmin pathway. In immunology, cytokine redundancy refers to multiple cytokines exerting similar actions. Consistent with this principle, targeting all 3 alarmins (TSLP, IL-25, and IL-33) was found to be more effective than blocking a single alarmin in chronic models of helminth infection and T2 cytokine–driven lung inflammation [86]. In addition, results from a murine model showed that both IL-33 and TSLP were required for IL-25 expression in epithelial cells, mucus metaplasia, and ILC2 expansion after rhinovirus infection [87].

In contrast, Sverrild et al [88] demonstrated that blocking TSLP signaling with tezepelumab in patients with uncontrolled asthma improves host tolerance to virus stimuli by reducing the alarmin IL-33 in BAL fluid. Moreover, tezepelumab decreased IL-33 expression and release in bronchial epithelial cells with and without in vitro viral stimulation [88]. Although relevant, these studies do not clarify the complex interplay between the different alarmin pathways. Future research should aim to explore these interactions, as well as the implications of blocking multiple alarmins.

Finally, it remains to be proven in clinical trials whether tezepelumab can attenuate virus-induced symptoms in asthma. Ex vivo evidence seems to suggest that TSLP could play a relevant role in viral exacerbations [88,90], which might be mitigated using TSLP antagonists. The reduced airway epithelial inflammatory response to viral challenge in BAL samples from patients with uncontrolled asthma treated with tezepelumab further supports this hypothesis. Notably, since this effect was achieved without compromising antiviral host resistance [88], interest in the non-T2 effects of tezepelumab has grown.

Who is the Optimal Responder to an Anti-TSLP Biologic?

To date, blocking TSLP has shown promising effects on clinical outcomes and asthma biomarkers. However, further investigation is required to determine the specific patient population for whom this biological therapy would be most appropriate. As previously discussed, the reduction in AAER reported for tezepelumab is comparable to that seen with other approved T2-targeting biologics [91], despite the allegedly broader effect of tezepelumab on T2 mechanisms than the more limited effects of anti-IgE, anti-IL5, or anti–IL-4R mAbs. Additional criteria that are commonly used when deciding on severe asthma treatment (eg, blood eosinophils, FeNO, and IgE levels) do not seem particularly helpful in selecting this pathway over others, as no compelling evidence has indicated these biomarkers could help to identify the optimal responders.

However, there is a particular subset of asthma patients who might show an outstanding response to blockade of TSLP. TSLP has been linked to mucus hyperproduction through various mechanisms, including the well-described IL-13 and IL-13–mediated pathways [10,55] and mast-cell release products such as prostaglandins [36,92]. Reduction in mucus plugging has been reported in a subanalysis of the CASCADE study cohort, with significant—but probably not clinically relevant—changes in mucus scores [56]. Additional RCTs on patients with demonstrated mast-cell-driven mucus will surely complement these findings.

Conclusions

Epithelial alarmins play a crucial role in the pathogenesis of asthma and other allergic and nonallergic airway disorders by helping to initiate and amplify several inflammatory mechanisms associated with disease severity and asthma control. TSLP, in particular, has been identified as a key element in T2 and non-T2 asthma features, with extensive evidence in in vitro and animal models suggesting its participation in airway inflammation, airflow obstruction, mucus hyperproduction, and airway remodeling. As such, anti-TSLP mAbs have emerged as an attractive option for treating severe asthma, particularly when multiple inflammatory mediators are involved, as opposed to a single responsible element (eg, anti–IL-5 biologics for eosinophilic asthma). There is compelling evidence supporting the effect of tezepelumab, a human anti-TSLPR mAb, on clinical outcomes, asthma biomarkers, and airway mucus burden; however, there is a dearth of data in patients with low-T2 disease. Further research is required to analyze the effect of anti-TSLP and other antialarmins in this specific population.

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Conflicts of Interest

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