ROLE OF TSLP PATHWAY IN THE ORIGIN AND MANAGEMENT OF ASTHMA: A REVIEW

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Abstract

Asthma was a chronic respiratory condition affecting millions worldwide, characterized by airway inflammation, bronchoconstriction, and variable airflow obstruction. Despite advancements in treatment, asthma remained a significant public health concern. This abstract examined current management strategies for asthma, focusing on pharmacological interventions, patient education, and environmental modifications. Inhaler therapy, including bronchodilators and corticosteroids, remained the cornerstone of treatment, with newer biologic therapies offering targeted approaches for severe asthma. However, optimizing asthma management required a multifaceted approach, encompassing patient education, adherence promotion, and identification of triggers. Environmental modifications, such as allergen avoidance and smoking cessation, played a crucial role in reducing exacerbations and improving long-term outcomes. Additionally, personalized asthma action plans empower patients to monitor symptoms and adjust treatment accordingly, fostering self-management and reducing healthcare utilization. Collaborative efforts between healthcare providers, patients, and caregivers were essential to achieving optimal improving the quality of life for those who suffer from asthma and controlling the chronic ailment.

Keywords *: Asthma, Bronchoconstriction*

INTRODUCTION :

The most prevalent chronic lung illness, asthma is impacted by both environmental and genetic factors, and its morbidity and death are rising globally. Asthma is characterized by an accumulation of peribronchial leukocytes, especially eosinophils, which have been identified as the main cell responsible for bronchial mucosal damage induction and Airway hyper-responsiveness (Ahr) to stressful stimuli [1]. For children five years of age and up, enuresis is defined as the involuntary leakage of pee during sleep. When there is at least one episode of urine loss per month for at least three consecutive months, and after ruling out other organic diseases, the International Children's Continence Society (ICCS) defines enuresis. Chronic inflammation of the lower airways (LOA) is the cause of asthma, a diverse illness that presents clinically as repeated bouts of coughing, dyspnea, wheezing, and chest tightness. According to the WHO, the prevalence of asthma varies by nation, from 1 to 18% [2]. As of right now, the most effective ways to manage asthma are to accurately measure how severe the condition is, employ β2-adrenergic agonists (bronchodilators for sudden attacks), and use anti-inflammatory medications such inhaled corticosteroids [3]. Additionally, the Global Initiative for Asthma (GINA) highlights that a crucial element of an effective asthma-management approach is evaluating the preferences and goals of the patient [4]. According to the 2002 GINA report, "it is reasonable to expect that control of the disease can and should be achieved and maintained in the majority of patients with asthma" [5]. Children with poorly managed asthma experience severe morbidity, mortality, and socioeconomic issues [6]. Asthma patients can be assessed for non-adherence using a variety of techniques, such as reviewing dispensing records, administering questionnaires, weighing canisters, or just asking patients if they are taking their prescribed medication. However, it is well known that these techniques frequently overestimate actual adherence rates [7]. Physicians can make the best diagnosis, choose the best course of treatment, and keep a closer eye on asthmatic patients by examining the particular kind of inflammation in their airways. Because it is highly correlated with type 2 inflammation, fractional exhaled nitric oxide (FENO) is a noninvasive, point-of-care, simple to use biomarker of airway inflammation utilized in the diagnosis and treatment of asthma [8]. Uncontrolled asthma can lead to a number of detrimental consequences that the sufferer must deal with, including a low quality of life and poor mental health [9]. Despite recent advances in developing research to better understand the pathophysiology of asthma, there are still no proven treatments for the condition [10].

TSLP, Chronic airway illnesses including asthma and chronic obstructive pulmonary disease (COPD) have been connected to TSLP, a crucial pro-allergic cytokine. Patients with asthma and COPD have high amounts of TSLP in their bronchial mucosa, which may indicate that TSLP has a biological function other than that of a "pro-allergic" or "Th2-favoring" cytokine. Airway structural cells, in addition to inflammatory cells, are targets and producers of TSLP, indicating the possibility of an autocrine loop that might significantly impact airway remodelling and the local inflammatory response. The several pathways that mediate the TSLP/TSLP receptor-signalling network in chronic airway disorders [11]. TSLP is essential for the proliferation of naïve CD4+ T lymphocytes. TSLP may facilitate this process through DC activation, although CD4+ T cells appear to be the more significant target for TSLP. TSLP had no, if any, direct impact on CD4+ T cells' ability to produce cytokines, but it did affect DCs' ability to produce IFN-γ [12-13]. the significance of TSLP, which also contributes to a reduction in lung inflammation. The development of an inflammatory response in the lung depends on TSLP signaling, and TSLP may be a useful target for regulating inflammation [14].

Background:

A significant global health issue that affects up to 235 million people globally is asthma The disease's pathogenesis is intricate and varied, including interactions between the host and environment at different scales, ranging from genes to organs [15]. Enhanced asthma control and increased patient adherence can be attained via the use of technology in asthma monitoring and management [16]. Asthma is a serious global health concern that impacts both children and adults [17]. subsequently asthma is a chronic condition, treatment for it must be ongoing and all-encompassing in order to minimize the probability of adverse events including exacerbations, fixed airflow limitation, and side effects from medication, and to reduce the symptom burden and good symptom control while maintaining normal activity [18]. Despite several efforts, no clinically accessible diagnostic tool exists to distinguish asthmatic children from children with transient wheezing at preschool age. This may result in children who outgrow their symptoms being over treated, and it may result in children who turn out to have asthma being undertreated [19]. One of the highest rates of chronic respiratory diseases (CRD) mortality in the World Health Organization's European Region is found in Central Asia, which includes five former Soviet countries: Kazakhstan, Kyrgyzstan, Tajikistan, Turkmenistan, and Uzbekistan [20]. A better understanding of how allergen exposure led to the early reaction (release of chemical mediators from airway mast cells) and the late reaction (recruitment of eosinophils, basophils, and mononuclear cells), which was linked to increased reactivity of the airways to irritant stimuli (bronchial hyperresponsiveness, or BHR), emerged in the 1980s. The mast cell stabilizing drug sodium cromoglicate decreased both the allergen-induced early and late bronchoconstrictor responses, which was also explained by the allergic scenario for asthma. In the 1970s, clinical trials also demonstrated that inhaled corticosteroids specifically, dipropionate were effective. When taken regularly, BDP was a very successful asthma controller medication. The finding of BDP eliminated the late asthmatic reaction and its accompanying BHR with allergen, as well as reducing airway eosinophilic, mast cell, and mononuclear cell inflammation and provided a molecular explanation for their effectiveness in managing daily asthma [21].

Epidemiology :

Asthma has a complex etiology, and each patient's clinical presentation is unique. A small percentage of asthmatic patients exhibit inflammation of the airways, primarily involving neutrophils. It is widely accepted that both genetic and environmental factors play a role in the pathogenesis of bronchial asthma, even though the exact cause of the condition is still unknown. Indoor allergens (such as dust mites, pets, and cockroaches), outdoor allergens (such as pollen and dust), sources of infection (such as pathogenic fungi, bacteria, and parasites), occupational pollutants, or food additives are examples of environmental substances that can trigger asthma. A Genome-Wide Association (GWA) study found that over 100 genes were substantially linked to the arrival of bronchial asthma in terms of genetic factors [22]. Numerous studies have been conducted on the prevalence and features of asthma as a result of the recent significant increase in the condition's reported prevalence across the world. The worldwide Study of Asthma and Allergies in Childhood and the European Community Respiratory Health Survey are two significant worldwide programs that have collected data using validated questionnaires, one for children and one for young people. After phase I of the International Study of Asthma and Allergies in Childhood, which was conducted in most participating countries between 1991 and 1993, the prevalence of asthma increased significantly in many other areas of the world but remained stable or decreased in other areas for a mean of seven years. This increase was particularly noticeable in children aged 13 to 14 years old [23].

TYPES:

The population with asthma has been categorized as into "Type-2-high" and "Type-2-low" asthma in recent years due to extensive research on the underlying molecular mechanisms or endotypes of asthma. Increased eosinophil

counts, serum periostin, total IgE, and raised levels of interleukin (IL)-4, IL-5, and IL-13 are characteristics of "type-2-high" asthma, which also includes allergic and eosinophilic asthma. "Type-2-low" asthma, which includes neutrophilic, paucigranulocytic, and obese asthma, is defined as the absence of T2 biomarkers or eosinophilic increase [24]. Different Th cell-driven inflammatory responses and airway remodeling processes, such as Th2, T follicular helper (TFH), Th17, and Th1 cells, are present in the two asthma endotypes. Type 2 inflammation is mostly caused by Th2-pathway activation, which results in elevated levels of the cytokines IL-4, IL-5, and IL-13. While IL-4 and IL-13 are linked to goblet cell metastasis, airway smooth muscle (ASM) contractility, and airway hyperresponsiveness (AHR), IL-5 induces eosinophil activation, maturation, and recruitment. A growing body of research indicates that aberrant Th17 or Th1 cell immune responses are linked to "Type-2-low" asthma. The production of IL-17 by Th17 cells contributes to airway remodeling, neutrophil inflammation, and corticosteroid resistance in asthma [25].

Risk factor:

The persistent increase in asthma prevalence despite treatment advancements indicates that our understanding of the underlying causes of asthma remains inadequate.

Childhood onset asthma

Over 150 birth cohorts on asthma were established globally in the last three decades as a result of the so-called "asthma epidemic" being recognized, and the data acquired has greatly clarified the causes of pediatric asthma.

- Genetics
- Indoor allergen exposure
- Microbiome exposures
- Respiratory viruses
- Environmental tobacco smoke (ETS)
- Air pollution

Adult-onset asthma

Notwithstanding studies on asthma in children, there are surprisingly few long-term studies on adults that follow the progression of the disease from early adulthood for a sufficient amount of time. On the other hand, there are established risk factors for both the beginning and worsening of the condition.

- Smoking
- Obesity
- Occupational exposures
- Sex hormones
- Stress events
- Very late onset asthma
- Medication related asthma triggers [26].

Pathophysiology:

Aspects such as genetic mutations, pollutants infections, obesity, hormones, tobacco smoke, exercise, cold air, and systemic eosinophilia have been found to cause chronic inflammation of the airways, which in turn causes airway blockage and hyperresponsiveness. In order to promote chronic airway inflammation, the innate and adaptive immune systems are both activated in the immune pathophysiology of asthma [27]. Genetic predisposition, environmental exposures, and maybe changes in the microbiome and metabolites (low molecular weight chemicals in biologic systems) are the most likely causes of inflammation in the lower airway. Six Type 2 inflammations—named for the type 2 T helper cell lymphocyte—affect most asthmatics. Type 2 inflammation is associated with certain cytokine profiles (interleukin [IL]-4, IL-5, and IL-14) and inflammatory cells. Individuals with asthma who do not have a significant predisposition towards type 2 inflammation frequently react poorly to corticosteroids and might be challenging to treat [28]. Accordingly, hypoxia is a common side effect of any asthma attack, even mild ones that can be readily treated with relatively small amounts of extra oxygen. There may be a connection between more severe hypoxemia and the requirement for higher amounts of supplementary oxygen and shunt physiology. Hypercapnia is not usually observed for FEV_1 values higher than 25% of predicted normal, but in general, there is no correlation between airflow rates and gas exchange markers. Furthermore, paradoxical deterioration of gas exchange, while flow rates improve after the administration of β-adrenergic agonists is not uncommon. Although it is not a predictor of outcome, arterial blood gas analysis is crucial in the therapy of individuals with acute, severe asthma [29].

Management:

Accomplishing worthwhile symptom control and reducing the likelihood of exacerbations in the future, as well as fixed airflow restriction and medication side effects, are the long-term objectives of asthma therapy. In order to do this, developing a relationship amid the patient and the healthcare professional is essential, and better results have been linked to shared-care models, in which people actively participate in the treatment of their asthma. Reminiscent to this, it has been demonstrated that "control-based" management techniques enhance asthma outcomes. These strategies involve adjusting medication depending on the patient's response for both alleviating symptoms and averting the possibility of exacerbations and side effects [30]. In order to prevent exacerbations—a sudden, abrupt worsening of asthma symptoms that frequently necessitate medical attention right away and/or the use belonging to oral steroid therapy—and lower the risk of morbidity and mortality, the main objective of asthma management is to attain and maintain control of the disease. Pharmacologic agents that are frequently used to treat asthma can be divided into two categories: controllers, which are long-term, daily medications that primarily have anti-inflammatory effects to achieve control, and relievers, which are medications taken only when necessary to quickly relieve symptoms of bronchoconstriction. Long-acting muscarinic receptor antagonists (LAMAs), ICSs, leukotriene receptor antagonists (LTRAs), long-acting muscarinic receptor antagonists (LABAs), and biologic treatments such as anti-IL-5 and anti-IgE therapy are examples of controller pharmaceuticals. Inhaled anticholinergics and fast-acting beta2-agonists are examples of relief drugs [31].

Role of TSLP Pathway asthma management:

Role of TSLP in Allergic Airway Inflammation

Extensive research conducted on mouse models has yielded significant insights into the function of TSLP in the pathogenesis of allergic asthma. OVA-induced artificial arthritis (AAI) studies revealed elevated TSLP mRNA expression in the airway, but anti-TSLP therapy decreased mucus formation, inflammatory cell inflammation, airway inflammation, and the release of IL-4, IL-5, and IL-6 cytokines in the bone marrow ascites (BAL). The same experiments also showed that injecting microRNA-19b decreased remodeling and inflammation of the airways by inhibiting STAT3 signaling by downregulating TSLP. Intranasal anti-TSLP mAb treatment reduced airway inflammation, AHR, and the amounts of IL-4 and IL-5 cytokine release in the BAL in experiments utilizing HDM-induced AAI. Mechanistically, by blocking AKT signaling pathways, anti-TSLP stopped E-cadherin and b-catenin from being lost and from being redistributed in the HDM-induced asthmatic animals. According to a recent study, co-exposure to OVA and increasing doses of PM2.5 increases the amount of total silicoprotection (TSLP) in the lung, which in turn increases the amount of acute lung injury (AII). Without wild-type allergen-primed CD4+ T cells to support them, animals missing TSLPR (Crlf2−/− mice) are not able to mount strong Th2 cell effector responses and do not establish airway inflammation in response to inhaled allergen. According to the previously mentioned research, adoptive transfer of allergen-primed TSLPR-deficient Th2 cells to recipient mice prior to antigenic challenge led to a decrease in allergen-specific serum IgE levels and airway eosinophilia in comparison to mice that received WT, allergen-primed Th2 cells, suggesting a critical function of this cytokine in Th2 memory-recall responses. Notably, a very elegant work demonstrated that, depending on whether TSLP is operating on cells of the innate or adaptive immune branch, it exhibits different effects in models of airway inflammation employing numerous cell lineage-specific TSLPR-deficient mice. In comparison to exposure to HDM alone, recent investigations have demonstrated that co-exposure to diesel exhaust particles (DEP) and HDM increases BAL eosinophil, neutrophil, macrophage, and CD4+ T-cell levels [32].

Role of TSLP in Human Asthma

Patients with SA showed increased expression of TSLP in the airway lamina propria. The aforementioned TSLP single nucleotide polymorphism (SNP) rs1837253 was shown to be a susceptibility locus for adult asthma, and genome-wide association studies revealed that it positively linked with the risk of childhood-onset asthma. In the ventilation lamina propria of SA patients, there was an increased expression of TSLP [32]. Moreover, this expression was prognostic of future exacerbations of the illness. Furthermore, there was a positive correlation seen between the quantity of neutrophils and the TSLP levels in the BAL of asthmatics. Furthermore, a number of investigations have demonstrated elevated TSLP gene expression in the mucosa of the asthmatic airways and elevated TSLP levels in the BAL of individuals suffering from moderate-to-severe asthma [33]. Interestingly, moderate asthmatics' bronchial epithelium and submucosa showed noticeably increased expression of TSLP upon bronchial allergen challenge, which was linked with the degree of late-phase airway blockage. Significantly, higher TSLP levels and the subsequent spread of Th2 inflammatory responses were caused by elevated IL-4 levels, a cytokine that improves the permeability of airway epithelial cells [34]. Increased TSLP receptor expression on asthmatic alveolar macrophages was linked in previous investigations to a longer duration of the illness and worsened lung function [35]. E-cadherin was delocalized as a result of a substantial rise in TSLP protein expression levels following HDM stimulation of the 16HBE human bronchial epithelial cell line [36]. TSLP

treatment boosted mitophagy, enhanced mitochondrial complex activity, and produced reactive oxygen species (ROS) in the human cell line THP-1. According to other research, DEP exposure caused TSLP production in HBECs. Moreover, pro-Th2 phenotype was demonstrated in vitro by monocyte-derived dendritic cell proliferation co-cultured with DEP-treated HBECs, as evidenced by increased OX40 ligand surface expression and improved ability to stimulate CD4+ T-cell production of IL-5 [37]. In addition, compared to children with MMA and healthy adults, the sputum and serum of SA patients had higher levels of alarmins, such as High mobility box 1 protein (HMGB1), which was found to significantly decrease with CS therapy. Notably, HBECs treated with HMGB1 produce more TSLP, demonstrating how these two alarmins are related [38,39,40].

The fact that the US FDA authorized tezepelumab (Tezspire), a human monoclonal antibody (IgG2λ) that blocks TSLP's interaction with its heterodimeric receptor, for the treatment of asthma in 2021 highlights the essential role that TSLP plays in the pathophysiology of asthma [41]. Numerous clinical trials have confirmed tezepelumab's potential for therapeutic use. 2014 saw the publication of the first phase 1b randomised, double-blind, controlled trial evaluating tezepelumab's effectiveness in asthma patients [42]. The decrease in FEV1 and the hyperresponsiveness of the airways caused by methacholine were both considerably reduced by tesepelumab. The administration of tezepelumab in patients with moderate-to-severe asthma resulted in a significant reduction in the number of peripheral blood eosinophils, AHR, and disease exacerbation compared with placebo treatment in a phase II trial (the CASCADE trial; NCT03688074) [43]. Additionally, tezepelumab reduced illness exacerbations and enhanced lung function, asthma control, and health-related quality of life in individuals with severe, uncontrolled asthma as compared to placebo in a phase IIb trial (the PATHWAY trial; NCT02054130) [44]. Similarly, regardless of low eosinophil counts in the peripheral at baseline, tezepelumab significantly reduced the likelihood of asthma exacerbations in patients with severe, uncontrolled asthma when compared to placebo in a phase III study (the NAVIGATOR trial; NCT03347279). Additionally, individuals treated with tezepelumab saw improvements in lung function and a decrease in hospitalizations and ER visits [45]. A noteworthy finding of the long-term, randomized, placebo-controlled extension trial DESTINATION (NCT03706079) showed that giving tezepelumab for two years was well-tolerated and resulted in long-lasting, clinically significant reductions in exacerbations of severe, uncontrolled asthma in patients [46].

Conclusion :

An unhealthy relationship between our genes and the environment they are exposed to, particularly during prenatal and early infancy, is represented by asthma. The rising incidence of asthma across all age groups suggests that the current “asthma and allergy epidemic” is caused by an imbalance between our immunity and living environment, which results in airway inflammation in response to environmental exposures and frequently harmless proteins like allergens. Given the tight connection between chronic rhinosinusitis and asthma, otolaryngologists need to be well-versed in the diagnosis, treatment, and assessment of asthma as well as its etiologic causes.

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