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# Targeting TSLP in Severe Asthma: A Case-Based Exploration for the Pulmonologist

**Announcer Introduction**

This is CME on ReachMD! This CME activity, titled "*Targeting TSLP in Severe Asthma: A Case-Based Exploration for the Pulmonologist",* is brought to you by The American College of Chest Physicians and supported by an educational grant from Amgen, Inc. and AstraZeneca. Before starting this activity, please be sure to review the faculty and commercial support disclosure statements as well as the learning objectives. Here's your host Dr Navitha Ramesh, ICU Medical Director at UPMC Community Osteopathic and Program Director of the Critical Care Medicine Fellowship.

**Dr. Ramesh:**

Hello everyone. I have the pleasure of welcoming my colleagues to discuss the impact of TSLP on asthma clinical manifestations, symptomatology, and disease course. Joining me today are doctors Stephen Doyle and Sandhya Khurana.

Dr. Stephen Doyle is an Assistant Professor of Medicine and Associate Program Director of Pulmonary and Critical Care Medicine at Corwell Health Michigan State University College of Human Medicine. Dr. Doyle, welcome to the program.

**Dr. Doyle:**

Thank you very much for having me. I'm excited to be here.

**Dr. Ramesh:**

And Dr. Sandhya Khurana is a Professor of Medicine and Director of the Mary Parks Asthma Center at the University of Rochester Medical Center. Dr. Khurana, welcome to our program.

**Dr. Khurana:**

Thanks Dr. Ramesh, it's a pleasure to be with you.

**Dr. Ramesh:**

Thank you both. So, now to get us started, Dr. Doyle can you give us an overview of TSLP, or thymic stromal lymphopoietin?

**Dr. Doyle:**

Sure. TSLP is an epithelial cell-derived cytokine, or commonly called an alarmin, that is produced in response to some kind of proinflammatory stimuli, such as microbes, trauma, allergens, or some kind of pollutant in the external environment.

One of its main actions is it drives an allergic inflammatory response through its activity on a number of different innate immune cells, dendritic cells, mast cells, T- and B- cells, and ultimately upregulates the production of many cytokines from the Th2 cells. TSLP is highly expressed by all the airway epithelial cells during allergic inflammation, and it helps mediate the interactions between the airway structural cells and the immune cells with the external environment.

**Dr. Ramesh:**

That's a great explanation, Dr. Doyle. Now, Dr. Khurana, as we delve into the nuances of severe asthma, how would you identify or define severe asthma?

**Dr. Khurana:**
That's a great question Dr. Ramesh. So, I consider a patient to have severe asthma if they are experiencing uncontrolled asthma symptoms despite maximal guidelines-based stepped asthma therapy, and despite adherence to optimized therapy. The definition of severe asthma, that's been used most frequently, is the one solidified by the 2014 ERS and ATS Combined Severe Asthma Guidelines, and they define severe asthma as asthma that requires treatment with guideline suggested medications at GINA Steps 4 or 5 (most commonly this would be medium to high dose inhaled corticosteroids and a long-acting beta agonist, or a second controller therapy) for the previous year, or if they require systemic corticosteroids for more than 50% of the previous year to prevent their asthma from becoming uncontrolled, or if their asthma remains uncontrolled despite this therapy. But, inherent in this definition is the understanding that the diagnosis of asthma has already been confirmed objectively, the patient's adherence with their inhaled and oral asthma therapy has been reviewed, inhaler technique has been reviewed, and any identifiable triggers and comorbidities have been addressed and optimized.

Severe asthma is often associated with a number of other comorbidities such as sinonasal disease, gastroesophageal reflux disease, obesity, psychopathologies like anxiety or depression. And some patients who have this severity of asthma really are at risk for adverse outcomes, including hospitalization and death, so it's really important to understand and identify which of our patients with asthma would be at risk and have severe asthma.

**Dr. Ramesh:**
That was a great explanation, Dr. Khurana. Thank you. Now we're going to dive a little bit deeper and ask Dr. Khurana again if you could just elaborate on the pathophysiology of severe asthma.

**Dr. Khurana:**
So, asthma as you know is a result of very complex gene and environment interaction and severe asthma is really part of that spectrum. As We think about the genetic predisposition, so the predisposition to develop asthma starts even before birth. And then there are environmental exposures along our lifetime that play a role in development and progression of asthma. For example, early life exposure such as respiratory infections, environmental tobacco smoke exposure, antibiotic use, certain allergen exposures, they all can promote the development of asthma. And interestingly, there are some factors that can be protective. For example vaginal birth, or later birth order – people who have a lot of older siblings, farm exposure early in life, these can be protective. And there's also heritability identified, especially in early onset asthma, and the estimates of heritability range from 35 to about 70%.

Severe asthma does not always start in childhood. It may develop in childhood and then in some people it just progresses through their life. But it can also develop later in life in adulthood. And again, we've recognized increasingly the heterogeneity that's inherent in asthma. As you know, it is not monolithic, it has multiple phenotypes and endotypes largely based on the type 2 or non-type 2 inflammatory pathways. So, the type 2 inflammation in asthma, for example, is the allergic or eosinophilic inflammation where often there is increased eosinophils in airways. And type 2 asthma tends to respond favorably to anti-inflammatory therapy, including steroids, but non-type 2 asthma, usually the neutrophilic phenotype, is marked by increased neutrophils in the airways and it can often be less steroid responsive or steroid resistant.

Another hallmark feature of asthma is the airway hyperresponsiveness. We know that chronic inflammation leads to structural alterations, subepithelial fibrosis, hyperplasia of the goblet cells resulting in mucus hypersecretion, and then airway smooth muscle hypertrophy. And these changes result in chronic airflow limitation and airway remodeling, and a lot of work has been done looking at mucus dysfunction in asthma, and mucus scores on high-resolution CT scans that have been associated with frequent exacerbations. And then also the epithelial barrier itself, which is a part of innate immunity - epithelial barrier defects have been detected in severe asthma. So, the mechanisms are complex and can affect various components of the airways and start early in life.

**Dr. Ramesh:**
Thank you, Dr. Khurana for that wonderful explanation on the pathophysiology of severe asthma.

For those of you just tuning in, this is CME on ReachMD. I'm Dr. Navitha Ramesh and joining me today to talk about targeting TSLP in severe asthma are Dr. Sandhya Khurana and Dr. Stephen Doyle.

Coming back to you, Dr. Khurana, what proportion of asthma in adults is considered severe?

**Dr. Khurana:**
Yeah, that again is a really important question because, severe asthma, though it makes up for a small percentage of total asthma; when it comes to the morbidity and the healthcare costs associated with evaluating and treating severe asthma, it makes up for majority of that cost. Asthma is the most prevalent chronic respiratory disease worldwide, and in the U.S. itself, the last data from CDC suggests a U.S. prevalence of 7.7%. Interestingly, over 60% of adults with asthma – again this was a survey that is available on the CDC

website - had uncontrolled asthma. So, it's important to try and separate what's uncontrolled asthma from true severe refractory asthma because the gap between these two is adherence, inhaler technique, the appropriate guidelines-based step therapy that we mentioned earlier. So there have been a few studies that have been, completed looking at and trying to understand the true prevalence, or what proportion of patients with asthma truly have severe asthma. And this is estimated to be about 4 to 6%. There was an elegantly done study in the Netherlands by Hekking and Colleagues and they actually looked at the National Pharmacy Database and found that in that country 3.7% of adults with asthma had severe asthma.

**Dr. Ramesh:**
Thank you, Dr. Khurana. That was a very good overview. And now moving on to Dr. Doyle. What do we know about TSLP in patients with asthma?

**Dr. Doyle:**
Yeah, I think that's a great question and an important one. So, what we know, as I kind of mentioned earlier, TSLP is a response from the respiratory epithelial cells to some kind of irritating stimuli, whatever that may be. When we think of asthmatics, a good portion of them are allergic or some kind of eosinophilic response. What we found in asthmatics is that when we checked, there's increased levels of human TSLP messenger RNA, as well as TSLP proteins in the airways of those with asthma compared to controls. This is actually correlated with disease severity as well. These increased TSLP levels have been found with airway obstruction and also have been associated with glucocorticoid resistance. In addition, there was a study that looked at a single nucleotide polymorphism in human TSLP locus and found that this was actually associated with a protection from asthma, atopic asthma, and airway hyperresponsiveness.

**Dr. Ramesh:**
Thank you, Dr. Doyle. With that information in mind, how does this TSLP affect the asthmatic cascade?

**Dr. Doyle:**
Thank you for that question, that's a great one, and this is one of the most fascinating things about asthma is the physiology associated with this complex disease. So, TSLP can affect multiple different components of asthma; Our allergic eosinophilic component, our non-allergic eosinophilic,our non-eosinophilic, non T2-driven inflammation, as well as it can lead to some generalized structural changes in asthma.

So, to start with the allergic asthmatic component, TSLP upregulates the facilitating antigen presentation by dendritic cells to our CD-4 naïve T-cells. When this happens this can accelerate the differentiation from these CD-4 naïve T-cells to our TH-2 cells, which then leads to the release of IL-4, IL-5, IL-13, which can then lead to downstream effects where there's IGE switching in B-cells, degranulation of mast cells, the IL-5 cells can lead to increased eosinophilic production, and that all can drive that T2- inflammation.

When we focus on the non-allergic eosinophilic responses, what we see that TSLP has a role in, such as when you're exposed to viruses, bacteria, some kind of pollutants in the air, is it, along with the other respiratory epithelial cytokines such as IL-33 and 25, it activates group 2 innate lymphoid cells. These cells can then lead to the production of IL-5, which can also lead to more eosinophilic response and can also lead to IL-13, which can be associated with the hypersecretion and airway hyperresponsiveness.

But the interesting thing about TSLP is that there is also a role in non-eosinophilic asthmatics, and the non-T2- inflammation. This can occur when environmental insults that were describe earlier lead to increased neutrophils in the airway. And the thought of this is that TSLP has an activity on the naïve T-cells that can be differentiated into IL-17 that then leads to neutrophilic production of asthma. So, there is an effect of TSLP that can lead to the neutrophilic asthmatics as well.

And finally, when we're looking at all of these structural changes that can occur with chronic asthmatic patients and remodeling of the airways, TSLP has been found to stimulate some human lung fibroblast cells that leads to the production of collagen that can promote this airway remodeling. So, as you can see in the asthmatic cascade, there are numerous ways that TSLP is associated in this and factors into how our asthmatics physiology presents itself.

**Dr. Ramesh:**
That was a really thorough in-depth explanation, Dr. Doyle. Thank you. So, what role do the airway or the respiratory epithelial cells, or cytokines, have in TSLP?

**Dr. Doyle:**
Yeah. So, kind of going into that, the airway epithelium is constantly involved in our immune surveillance. It really leads as a barrier between our internal environment and our external environment, and it's constantly being exposed to an enormous amount of different allergens, noxious particulate matter, microbes and a lot of other pollutants. These epithelial cells lead to intracellular junctions that have adhesive forces to try to maintain the integrity of that epithelial barrier. However, when our body gets exposed to some of these

allergens or pollutants it does release the cytokines, which is the alarming cells I mentioned earlier, such as TSLP IL-33 and IL-25. And these do is they lead to the rapidly released, after this non-program cell death of these epithelial respiratory cells that leads down to both the innate and the adaptive immune response that I talked a little bit about previously. So, they have a paramount role in protecting us from our environment, and then ultimately leading to poor asthmatic control.

**Dr. Ramesh:**
Thanks again, Dr. Doyle. That was very, very good. With that background in mind, is TSLP blockade beneficial in patients with asthma?

**Dr. Doyle:**
That's a great question as well because ultimately the physiology can be great, but our whole goal here is to try to find some kind of treatment or therapy that is going to help our asthmatic patients. So, researchers have looked at this and what they've done is developed a monoclonal antibody against thymic stromal lymphopoietin, or TSLP, and it started with a proof-of-concept study in mild allergic asthmatic patients. And what they did is they provided the medicine of the monoclonal body anti-TSLP or placebo, and they looked at multiple different allergic responses, methacholine challenges, fractional excretion of nitric oxide, eosinophilia and such. And what they found in this proof-of-concept study was that treatment with the anti-TSLP monoclonal antibody, there was reduced allergen, reduced bronchoconstriction, and most of the indexes of airway inflammation were improved before and after different challenges. This led to the PATHWAY trial which was a phase 2 study of a double-blinded placebo-controlled trial comparing tezepelumab with placebo at different doses over a 1-year period. And what the researchers found was that there were lower rates of clinically significant asthma exacerbations, and kind of an important endpoint of this is that it was really independent of the blood eosinophil count. So, they noticed that regardless of what the eosinophils were, there was still some improvement in clinically significant asthmatic exacerbations.

And this led to the phase 3 NAVIGATOR trial, which looked at comparing tezepelumab at a dose of 210 mg compared to placebo for 52 weeks. The primary endpoint during that study was annualized rate of asthma exacerbations for the severe uncontrolled asthmatics that were enrolled in the trial.

The study importantly found there were fewer exacerbations, but there was also better lung function, asthma control, and health related quality of life compared to placebo, which is obviously a very patient-centered outcome that was able to be found. So, there has been multiple candid trials that have shown that TSLP blockade has become beneficial in asthmatics.

**Dr. Ramesh:**
Thank you again, Dr. Doyle. So, it's really wonderful discussion about TSLP in asthma, and as we come to the end of our discussion, what are your key takeaways for our listening audience? We'll start with you Dr. Khurana.

**Dr. Khurana:**
Yes. Thank you Dr. Ramesh, and this is really a great overview of the TSLP pathway and a summary of the anti-TSLP antibody trials by Dr. Doyle. You know, my key takeaways from this is I think, is that asthma is a complex disease. And the burden is high, and we're really fortunate to have now access to these advanced therapies for patients who have truly severe asthma, and it's become increasingly important to really separate uncontrolled from difficult to treat from severe asthma, so we can truly identify patients who are at the greatest risk of poor outcomes, and are most likely to benefit from these advanced therapies. B it's really an exciting time to be in the field of asthma, and to be, , to be able to provide or offer, in partnership precision medicine to our patients who are suffering from just uncontrolled symptoms.

**Dr. Ramesh:**
Thank you, Dr. Khurana. Dr. Doyle, what are your key takeaways for our listening audience?

**Dr. Doyle:**
I agree with Dr. Khurana on this. Asthma is a very multifactorial and complicated disease, and as we learn more and more about this fascinating physiology, it really gives us more potential treatment options for our severe asthmatics. And what we can do at the bedside is be looking at these clinical presentations and surrogates of different types of inflammation that we can get based off laboratory studies or clinical history or exposures, and then we can tie that into this asthmatic cascade and kind of see where it fits. And as we're getting more treatments for these severe asthmatics, we can provide different therapies. And that's just the fascinating thing about this disease process is that we're learning more and more about how the body interacts with all of these different types of exposures and becoming better about developing better treatment options for those. So, I'm very optimistic for the future that we're going to continue to have improved therapies that are going to provide benefit to our patients.

**Dr. Ramesh:**
That's wonderful. Thank you, Dr. Doyle. So, yes, precision medicine, and different therapies for asthma down the pipeline. It's very

exciting for all of us who take care of asthma patients. Thank you both so much for your time today. I thoroughly enjoyed our conversation and hope our listening audience learned from our conversation as well. Dr. Doyle and Dr. Khurana, thank you for joining me.

**Dr. Khurana:**
Thank you for having us.

**Dr. Doyle:**
Thank you.

**Dr. Ramesh:**
I'm Dr. Navitha Ramesh. Thank you for listening.

**Announcer Close**
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