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Where are the New Targets in Severe Asthma? Looking Upstream in the Inflammatory Cascade

Announcer:
Welcome to CME on ReachMD. This replay of a live broadcast titled “Where are the New Targets in Severe Asthma? Looking Upstream in the Inflammatory Cascade”, which is provided by National Jewish Health, and is supported by an educational grant from AstraZeneca Pharmaceuticals.

Dr. Wechsler:
Hi. I’m Mike Wechsler, Professor of Medicine and Director of the Cohen Family Asthma Institute at National Jewish Health in Denver, Colorado. I’m joined by my colleague, Eileen Wang, who’s Assistant Professor of Medicine in the Division of Allergy and Clinical Immunology here at National Jewish Health. Our learning objectives today are to define the epithelial alarmins and their pivotal role in inflammation asthma, to describe how the epithelial alarmins impact both T2 and non-T2 downstream inflammation asthma, to explain how therapies such as anti-TSLP would be expected to modulate airway inflammation in patients with either a T2-high or T2-low phenotype, and to evaluate the results of clinical trials of novel therapies that target the epithelial alarmins.

Now, I’ll turn it over to Dr. Wang, who will kick off today’s program by discussing the types of severe asthma inflammation.

Dr. Wang:
Thank you so much, Dr. Wechsler. So, asthma is a highly prevalent disease with a high disease burden. There are over 25 million Americans affected by asthma; 41% of these reported having had at least one asthma exacerbation in the last year. There are 1.6 million asthma-related emergency departments visits in the last year. And on average, about ten people die from asthma each day. In the last year, there were also about 180,000 asthma-related hospitalizations. So, severe asthma accounts for a disproportionate amount of asthma costs to society. While severe asthma represents only about 10% of the asthma population, they incur over 60% of costs. Looking at data from 2002 to 2007, indirect costs of severe asthma was estimated to be about $6 billion. This includes the cost of work and school days lost and loss of productivity. Direct costs were estimated to be between $50 to $80 billion per year, and this includes prescription medications, office space visits, emergency department visits, and inpatient visits.

The European Respiratory Society and American Thoracic Society defines severe asthma as use of high-dose inhaled corticosteroids plus a long-acting beta agonist or leukotriene modifier or theophylline for the previous year or system corticosteroids for 50% or greater of the previous year, and this equates to GINA steps 4 and 5 therapy. And this is to prevent asthma from being uncontrolled or which remains uncontrolled, despite this therapy.

Uncontrolled asthma is defined as having two or more exacerbations requiring oral corticosteroids in the last year, a serious exacerbation of one or more that requires hospitalization, ICU stay, or mechanical ventilation the previous year, or persistent airflow limitation, defined as an FEV1 less than 80% predicted. In evaluating severe asthma, it’s important to assess comorbidities and also assess adherence in technique.

So, severe asthma is immunologically very complex. Our understanding of inflammatory mechanisms or endotypes and pathobiologic features of severe asthma has grown significantly in the last few years. Looking on the left-hand side, we have type 2 inflammation, or type 2 endotype. And this involves effector cells to include T-helper 2 cells or Th2, innate lymphoid cells or type 2 or ILC2s, mast cells,

b-cells and eosinophils. On the right-hand side, you'll see non-type 2 inflammation, or non-type 2 endotype and that typically involves a Th1 and Th17 pathway that leads to neutrophilic inflammation. These then lead to hyperresponsiveness, error remodeling, mucous production, and smooth muscle constriction and hypertrophy in asthma.

In terms of the inflammatory subtypes of asthma, so based on biomarker analysis of airway inflammation, via self-counts in sputum, BAL, bronchial biopsies, fractional exhaled nitric oxide, peripheral blood eosinophils, and environmental air allergen sensitization, asthmatic patients can be classified into four unique phenotypes; eosinophilic asthma, which can be allergic or non-allergic, mixed granulocytic asthma, with both eosinophils and neutrophils, neutrophilic asthma, and paucigranulocytic asthma.

So, eosinophilic phenotypes fall into a type 2 asthma type endotype, whereas neutrophilic or paucigranulocytic tend to be associated with a non-type 2 endotype. However, it is important to recognize phenotypic heterogeneity and instability lead to exceptions of this general correlation. For example, there are non-eosinophilic, but type 2 atopic asthmatics who demonstrate a paucigranulocytic phenotype. In addition, phenotypes and endotypes in the same asthmatic may vary over time due to natural history of the disease or as a consequence of treatment. Further research is required to understand these relationships. It's also w- important to understand that these endotypes are a spectrum.

Delving further into the inflammatory subtypes of asthma, looking at type 2 high endotype, you can see an allergic or eosinophilic phenotype. Key biomarkers and cytokines you can see in this type of asthma include elevation of blood eosinophils, increased BAL or sputum eosinophils, increase exhaled nitric oxide, increased total serum IgE, you can also see environmental air allergens sensitization with clinical relevance, and IL-4, 5, and 13 can be implicated in this type of asthma. For the type 2 low endotype of asthma, you can see a neutrophil-like phenotype. You will k- see here, typically, increased BAL or sputum neutrophils and the key cytokines that you'll see here are interferon gamma, IL-1 beta, IL-6, 8, 17, and TNF alpha.

Then there's a paucigranulocytic phenotype under the type 2 low or non-type 2 endotype of asthma. Here you'll see normal BAL and sputum neutrophils and eosinophils. You'll also see an uncoupling of this airway obstruction from airway inflammation. And this is thought to du- be due to multiple different mechanisms.

For the last category, you'll see a mixed endotype. So, you'll see mixed granulocytic inflammatory markers, and that includes increased BAL and sputum eosinophils and neutrophils.

Now, looking at type 2 high asthma, again, you'll have an eosinophilic, allergic, or both an eosinophilic and allergic phenotype. This probably accounts for more than half of asthma patients. This is driven by T-helper 2 cells and the innate lymphoid cells, type 2 or ILC2s. And again, you'll see this characterized by type 2 cytokines. So, specifically IL-4, IL-5, and IL-13. IL-4 leads to production of IgE and the activation of mast cells. IL-5 leads to the activation and recruitment of eosinophils, and IL-13 leads to mucus production, excelled nitric oxide production, airway hyperresponsiveness, and remodeling. Typically, this endotype of asthma are good responders to corticosteroid treatments.

Now, looking at the allergic phenotype of type 2 high asthma, you can see that IL-4 and IL-13 are active players. They activate the B-cell, which then leads to binding on multiple different effector cells including mast cells, which lead to mediator release, which includes histamines, leukotrienes, and cytokines. This then causes physiologic effects. You can see the early response with bronchospasm, edema, and airflow obstruction, but also a late response with airway inflammation, airflow obstruction, and airway hyperresponsiveness.

For the eosinophilic phenotype of type 2 high asthma, not all eosinophilic asthma is driven by allergic triggers. It's important to note that there are infectious agents and irritants that can stimulate the innate immune system and this is via IL-33 and IL-25, which then also stimulates ILC2 and Th2 cells. It's also important to note that the degree of peripheral eosinophilia does not correlate perfectly with lung eosinophilia and does not directly predict response to therapy.

Now, flipping sides to the neutrophilic phenotype under type 2 low asthma. So, neutrophilic predominance is what you'll see with mostly sputum i- or BAL neutrophils, greater than or equal to about 40 to 60%. This can be associated with oxidative stress, chronic infection, smoking, and a high fat diet. There's generally poorer response to corticosteroids, higher associations with fixed airflow obstructions. In addition, airway epithelial cells can produce cytokines that stimulate Th17 cells, which attract and stimulate neutrophils. There's also Th1 cells that are stimulated by innate immune stimuli to drive neutrophilic inflammation. Looking at the airway microbiology, you can see a greater frequency of pathogenic taxa and high relative abundance.

Lastly, for the paucigranulocytic phenotype under type 2 low asthma, there is no evidence of increased eosinophils or neutrophils in this type of asthma. Therefore, it's considered to be non or low inflammatory. This type of asthma is poorly understood and less well-characterized. You can sometimes see airflow limitation as the result of structural changes and airway remodeling, therefore, there's an uncoupling from airway inflammation. You can see collagen deposition and smooth muscle proliferation. You can also see persistent airway hyperresponsiveness and it's thought to be potentially, steroid-insensitive.

Now, in summary, asthma's a highly prevalent condition with a high disease burden. Severe asthma accounts for a disproportionate amount of asthma cost to society, and therefore it's an extremely important public health issue. It's important to distinguish asthma severity from asthma control and to address secondary factors leading to poor asthma control, which include adherence, technique, and other comorbidities. There are several subtypes of asthma, which include type 2 high, which is characterized by eosinophilic and/or allergic inflammation, type 2 low, characterized by neutrophilic and/or paucigranulocytic inflammation, or a mixed phenotype with features of both.

Now, I'll turn it over to Dr. Wechsler to discuss the role of epithelial alarmins in severe asthma inflammation.

Dr. Wechsler:
Thank you, Eileen. Now let's discuss connecting the role of epithelial alarmins to severe asthma inflammation. First of all, it's important to recognize the important role that the airway epithelium plays in asthma. The airway epithelium is the first continuous line of defense against inhaled insults. It has a very large surface area that comes into contact with 10,000 liters of inhaled air every day. The epithelium is a key source of inflammation in asthma. Epithelial cytokines, such as TSLP, IL-33, and IL-25 are rapidly released in response to various insults initiating multiple inflammatory cascades. The airway epithelium is also significantly altered in asthma. Goblet cell hyperplasia and increased mucus production lead to airway blockage, decreased epithelial-type junction numbers and integrity allows external insults to really penetrate the airway wall. And increased epithelial thickness results in airway narrowing, as well. Furthermore, subepithelial inflammation and fibrosis can lead to fixed airflow obstruction. And lastly, there can be increased inflammatory cells, o- mast cells, and eosinophils that are impacted by the epithelium.

So, the key roles that the airway epithelium plays in asthma are, it plays a role as a barrier and as a sensor, it's a protective barrier and environmental sensor that really identifies different insults that affect the epithelium. It also mediates immunity. It drives both the innate and adaptive immune responses. The epithelium also induces inflammation by releasing the epithelial cytokines, the alarmins, that activate airway inflammation upstream. And the airway epithelium also drives structural changes, which is a starting point for airway remodeling.

The airway epithelium produces the alarmins that drive asthma inflammation from the top of the inflammatory cascade. TSLP, IL-25, and IL-33 all play an important role in driving downstream inflammation. And these alarmins play a role in terms of allergic inflammation, it's mediated by mast cells and IgE. It plays a role in eosinophilic inflammation that's mediated by IL-5 and IL- eosinophilic trafficking, mediated by IL-4 and 13. It also plays a role to some extent in neutrophilic inflammation, and in terms of structural changes, in terms of interactions with a variety of different fibroblasts.

So, which are the alarmins? Well, the alarmins are all epithelial cytokines that get released in response to different environmental insults. They get released after epithelial damage or immune cell activation, and they activate downstream innate and adaptive immune responses. IL-33 is one of the key epithelial cytokines. It has a large number of cellular targets and it can augment both Th2 and non-Th2 responses. TSLP is also an important alarmin, with also a large number of cellular targets that drives Th2 responses by both dendritic cells and T-cells and can also impact structural changes in a variety of different cells. Lastly, IL-25 has a smaller number of cellular targets and requires IL-4 to drive Th2 response.

So, in summarizing the key points, airway epithelium plays a critical role in asthma, it plays a role as a barrier and a sensor, it mediates immunity, it induces inflammation, and drives structural changes, and it also play an important role in allergic, eosinophilic, and neutrophilic and structural changes.

Now, I'll turn it back over to Eileen to discuss epithelial alarmins and the inflammatory cascade in greater detail.

Dr. Wang:
Thank you, Mike. For discussion segment three, we'll be talking about how epithelial alarmins relate to downstream cytokines in the inflammatory cascade. So, looking at the role of alarmins in the immune response to aeroallergens we can think about protease dependent mechanisms and also protease independent mechanism. For the protease dependent mechanism, you have protease containing aeroallergens, this then disrupts the epithelial barrier by acting on tight junctions. Then epithelial cells sense the protease activity an induced release of inflammatory mediators. For the protease independent mechanism, allergens can lead to repeated or sustained activation of epithelial pattern recognition receptors. Allergens can also trigger endogenous danger signals such as ATP and uric acid. This then leads to the release of type 2 promoting cytokines. In vitro studies show that aeroallergen exposure can trigger epithelium release of TSLP, IL-33 and IL-25. Human studies show increased expression of these epithelial alarmins in the airway of epithelium of allergen-challenged individuals with mild atopic asthma, which correlated with increased airway obstruction.

Now delving deeper into TSLP, this is a key epithelial cytokinin asthma. Human TSLP was first described in 2001, while epithelial cells are the primary source of TSLP, other sources also include mast cells, dendritic cells, fibroblasts, and airway smooth muscle cells.

TSLP initiates multiple downstream innate and adaptive immune responses involved in asthma inflammation. Variance at the TSLP gene loci had been associated with asthma risk. TSLP is central to the regulation of type 2 immunity and also involved in non-type 2 immune responses. The expression of TSLPs increased in the airways of patients with asthma an correlates with Th2 cytokine and chemokinic expression and disease severity. TSLP can also affect the neutrophilic inflammatory pathway and you can see this is the Th1 and Th17, which then induce neutrophilic inflammation.

It's important to note that TSLP drives changes in airway structural cells. So, it has direct effects on fibroblasts, which may contribute to airway remodeling, airway mast cells are activated by TSLP and can promote a cycle of TSLP driven structural changes, and TSLP also stimulates airway smooth muscle cells, which in turn can promote airway inflammation.

So, there are multiple clinical features of asthma that are associated with TSLP. And this ranges from asthma severity, reduced lung function, potential airway remodeling, reduced steroid response, and exaggerated response to viral infections.

Now, looking at IL-33 and the immunobiology, IL-33 is a member of the IL-1 superfamily. Like other members of this family, IL-33 is expressed as a full-length precursor located in the nucleus. Triggers for rapid release of immunologically active full length IL-33 from epithelial cells include epithelial injury or exposure to environmental stressors such as allergens, viruses, or other inducers of epithelial stress, or damage. Various allergens with protease activity including house dust mites, Alternaria, aspergills fumigatus, and pollens can induce full length IL-33 release and subsequent cleavage into its active form. Intrinsic proteases such as from damaged airway epithelial cells and extrinsic proteases such as those of allergens can enhance IL-33 activity through their proteolytic activities.

IL-33 binds to heteradenic receptor formed by IL-1 receptor like 1, also known as ST2, and the IL-1 receptor accessory protein. Activation of this receptor leads to activation of an NF kappa B and MAPK signaling pathways. IL-33 activates ST2 expressing immune cells involved in type 1 and type 2 immunity and this includes ILC2s, Th2 cells, mast cells, eosinophils, basophils, and dendritic cells. It can induce type 2 cytokine productions, specifically IL-5 and 13 in both an IL-4 dependent and independent manner. Through its effect on ILC2s and other innates cells, IL-33 can induce type 2 responses independently of Th2 cells. In the presence of IL-12, IL-33 can also enhance an interferon gamma response.

Now, looking at IL-33 and its relevance in asthma, there are several genetic studies that have demonstrated significant associations between genetic variants of IL-33 and ST2 in human asthma. IL-33 has been shown to be up-regulated in the airway epithelium and BAL fluid from individuals with moderate-to-severe asthma. Release of IL-33 is increased during experimental rhinovirus-induced asthma exacerbations. Clinical phase 2 trials with monoclonal antibodies targeting either IL-33 or ST2 are currently undergoing.

Now, shifting gears to IL-25 and looking at the immunobiology, IL-25, which is also known as IL-17E is a member of the IL-17 cytokine family, consists of 6 structurally related, but functionally distinct proteins. IL-25 is unique among members of this family in that it promotes type 2 immune responses including eosinophilic inflammation and overproduction of IL-4, 5, and 13. IL-25 binds to heteradenic receptor known as IL-17 receptor A and IL-17 receptor B, otherwise known as IL-25 receptor, which is expressed on several cells of the innate and adaptive immune system, including ILC2s, activated memory Th2 cells, TSLP activated dendritic cells, mast cells, eosinophils and endothelial cells. This induces Th2 mediated airway inflammation, airway hyperresponsiveness, and airway remodeling, with evidence of goblet-cell hyperplasia, substituted-epithelial collagen deposition, and angiogenesis.

Now, looking at IL-25 and its relevance in asthma, there was a study of steroid naïve, newly diagnosed asthmatic individuals and healthy control subjects. They looked at bronchoscopy, sputum, and blood data. They found that those with high IL-25 had severe airway ir- eosinophilia, marked substituted-epithelial fibrosis, higher expression of MUK5AC and elevated IgE levels. Plasma IL-25 levels correlated with epithelial IL-25 expression. This suggests that IL-25 may serve as a potential biomarker. There's evidence for allergen and viral induced release of IL-25 in asthma. However, there are no human clinical trials of i- anti-IL-25 antibodies at this time.

Now, we'd like to show you an animation to illustrate the inflammatory cascade and epithelial alarmins.

Announcer:
In asthma, the inflammatory cascade is thought to begin at the airway epithelium. Here, triggers like allergens, parasites, fungi, viruses, proteases and other irritants, such as pollutants and smoke can lead to the release of cytokines such as TSLP, IL-25, and IL-33. These cytokines termed "alarmins" initiate the release of downstream cytokines from cells of both the innate and adaptive immune system. Initially, the main cells being triggered are innate lymphoid cells, also known as ILC2 cells. T-cells are subsequently activated and can differentiate into Th1, Th2, or Th17 cells, depending on whether they are stimulated by IL-4, IL-12, or IL-6, respectively, in addition to other cytokines. The adaptive immune response initiates when t-cells are activated in an antigen-specific manner and communicate with b-cells for antibody production. Triggering of either ILC2 cells, or Th2 cells leads to type 2 inflammation, characterized by the release of IL-4, IL-5, and IL-13, the major type 2 cytokines. IL-5 is the primary cytokine driving eosinophil differentiation. Proliferation, recruitment, maturation, and activation. IL-13 also activates eosinophils, as well as basophils, goblet cells, and type 2 macrophages, which

contribute to mucus production and remodeling, two key aspects of asthma. IL-4 is responsible for isotype switching of the b-cell toward production of IgE. IgE will then bind to its Fc epsilon receptor on the surface of mast cells and basophils. When exposed to a specific antigen, these IgE molecules and their receptors will cross-link and lead to activation of these cells and release of their contents, including histamines, leukotrienes, prostaglandins, and type 2 cytokines. When Th1 cells are triggered, interferon gamma is the major cytokine produced, which leads instead to the recruitment of macrophages. The release of CXCL9 leads to neutrophilic inflammation. Th17 cell activation can also lead to neutrophilic inflammation, primarily through the release of CCL2 and CCL10.

Dr. Wang:
For our key points, epithelial alarmins are epithelial derived cytokines that act upstream in the inflammatory pathway of asthma. Alarmins can be activated by many triggers, including allergens and viruses. TSLP is an upstream epithelial cytokine that acts through ILC2 and t-cells to trigger eosinophilic in- allergic inflammation, structural changes, and possibly even neutrophilic inflammation. IL-33 is an alarmin that can activate both type 1 and type 2 immune responses by activating many cell types thought to be key in driving the inflammation int he asthmatic lung. Lastly, IL-25 is an important alarmin responsible primarily for type 2 immune response.

And now, Mike will discuss targets for current and emergent treatments in severe asthma.

Dr. Wechsler:
Thank you, Eileen. In 2021, global initiative for asthma guidelines recommend add-on type 2 targeted biologic therapy except 5, once patients have already received inhaled corticosteroids, long-acting beta agonists, and potentially other controllers such as long-acting muscarinic agents or leukotriene modifiers. Novel asthma therapies that have currently been approved include anti-IgE therapy with omalizumab, anti-IL-5 therapies such as mepolizumab or reslizumab or anti-IL-5 receptor antagonists with benralizumab, and the anti-IL-4 receptor alpha therapy, which also blocks IL-13, dupilumab. However, it's exciting that there are several other novel therapies that are currently in development and hopefully will be approved in the coming years. These include anti-TSLP and anti-IL-33, both of which target these two important alarmins. Anti-IL-17 and anti-IL-6, which hopefully may play a role in terms of non-type-2 inflammation. JAK inhibitors also may play a role because they work downstream from a variety of different cytokines. And then other novel therapies include anti-M1 prime, anti-GATA3 DNAzyme, TLR9 agonists, CRTH2 e- or prostaglandin D2 antagonists, and even antibiotics are considered for use in patients with severe asthma.

So, what can we achieve with biologics; the ones we currently have available and the ones that are coming down the road? Well, our goal with utilizing biologics is to reduce exacerbations, to improve lung function, to reduce steroid dose and side effects, to improve symptoms and quality of life, and hopefully to disease-modify these patients with severe asthma to prevent asthma over the long term. Biologics can target many different asthma cytokines. The ones we currently have available can target IL-5, IgE, IL-4, and IL-13. Let's focus first on biologics that target IL-5. Mepolizumab and reslizumab target IL-5 and prevent in the activation, maturation, proliferation of different eosinophils. Benralizumab binds the IL-5 receptor and prevents IL-5 from binding to the IL-5 receptor and activating the eosinophils. All of these therapies reduce eosinophil numbers and have a significant impact in terms of reducing exacerbations, improving lung functioning, and even reducing corticosteroid dosing.

What about biologics that target IL-4 and IL-13? Well, dupilumab is a monoclonal antibody that targets the IL-4 receptor alpha. It prevents IL-4 and IL-13 from binding to the IL-13 receptor and it's indicated for broader type-2 inflammation. It has benefits in patients with eosinophilic asthma, allergic asthma, or high-nitric oxide in mediated asthma, and it's also indicated for patients with steroid-dependent asthma. It works downstream via JAK stat dependent pathways to prevent IL-4 mediated production of IgE, to prevent IL-13 in mediated nitric oxide and mucus production, and to prevent IL-4 and IL-13 mediated trafficking of eosinophils into the tissue and therefore has been shown to both reduce exacerbations and improve lung function and other asthma outcomes.

Well, what about blocking epithelial alarmins? Well, there's several potential targets that biologics can go after in terms of targeting epithelial alarmins. One of these is targeting TSLP upstream. As we've discussed, TSLP is an upstream cytokine, it's an epithelial cytokine, or alarmin that triggers the production of different type 2 cytokines, including IL-4, IL-5, and IL-13. Tezepelumab targets TSLP and blocks inflammation from the top of the inflammatory cascade. Tezepelumab is a human monoclonal antibody that binds to the TSLP, and specifically blocking it from interacting with its receptor. It has the potential to inhibit multiple downstream inflammatory pathways and enact broach effects on airway inflammation. Tezepelumab has been shown in both phase 2 and phase 3 studies to be an effective strategy for management of patients with severe asthma. In the phase 2 study that was published by Dr. Jonathan Corin the New England Journal of Medicine, tezepelumab resulted in significant reduction in analyzed asthma exacerbation rates for all tezepelumab groups compared with placebo. Interestingly, it was shown to be effective in a broad range of patients, in patients who had eosinophilic asthma, and non-eosinophilic asthma, in patients who had high nitric oxide and low nitric oxide, and in patients who demonstrated both a Th2 status and a low Th2 status. So, in the phase 2 study, it was really encouraging and led to the phase 3 studies.

The NAVIGATOR study was a phase 3 study that was published in 2021 in the New England Journal of Medicine with the lead author being Andrew Menzies-Gow. The study demonstrated that tezepelumab reduced exacerbations in patients with a broad range of inflammatory profiles; whether it was patients with high eosinophils or low eosinophils, patients with high exhaled nitric oxide or low nitric exhaled nitric oxide, and in patients who tested positive for perineal aeroallergen or who didn't test positive for any aeroallergen. So, for all these patients, eosinophilic high or low, nitric oxide high or low, or allergic, tezepelumab was effective in management of these patients. Tezepelumab also demonstrated a significant ability to reduce a variety of different key biomarkers that are important in asthma management. These included the fact that in NAVIGATOR study, tezepelumab reduced blood eosinophil counts significantly compared to placebo, it lowered exhaled nitric oxide levels significantly, and it also lowered serum IgE levels over the 52 week treatment period.

Another important tezepelumab study was the phase 3 SOURCE study, The goal of which was to demonstrate an efficacy of tezepelumab in terms of reducing oral corticosteroid dosing in patients who had oral corticosteroid dependent asthma. In this study, tezepelumab was effective in reducing the oral corticosteroid dosing in that 54% of patients were able to reduce the corticosteroids dosing by 90%. However, there was also a strong placebo affect and as many as 46% of patients who received placebo were able to reduce their corticosteroid dosing by 90 to 100%, as well. There weren't significant differences between tezepelumab and placebo in terms of the proportion of patients who were able to reduce corticosteroid dosing by 70 to 95% and the proportion of patients who had no change or any increase in corticosteroid dosing. The reason that there was no significant difference between tezepelumab and placebo in terms of reducing oral corticosteroid dosing may be due in part to the large placebo effect that resulted from possibly the long duration of the oral corticosteroid reduction phase and the ability to taper corticosteroids on multiple attempts, even after patients had an exacerbation. It's important to note however in this study, that a greater reduction in oral corticosteroid dosing was seen with tezepelumab versus placebo in patients who did have baseline eosinophil counts of greater than 150 or greater than 300 cells per microliter.

Lastly, another important study evaluating tezepelumab was the CASCADE study in which a bronchoscopy was performed before and after treatment with tezepelumab or placebo. In this study, it was demonstrated that tezepelumab resulted in a significant reduction in airway submucosal eosinophils in biopsies from patients with severe asthma. This is the first study to demonstrate a reduction in tissue eosinophils in patients with asthma. Importantly, as well, there was no significant reduction in airway neutrophils, T-cells, or mast cells.

So, what about blocking IL-33, another epithelial cytokine? Well, in 2021, a study was published in the Journal of Allergy Clinical Immunology that demonstrated that astegolimab, and anti-ST2 or anti-IL-33 therapy was shown to be effective and safe in adults with severe asthma. In this phase 2 study, it was demonstrated that different doses of astegolimab were able to reduce r- exacerbations in patients with severe asthma. It would be great to see more data emerge with this interesting molecule.

Another anti-IL-33 therapy is also in development. Itepekimab was demonstrated to reduce exacerbations versus placebo and had efficacy comparable to dupilumab, but interestingly, it was less effective in combination with dupilumab therapy. More data are to come with this study, as well.

Now, let's watch an animation that illustrates connecting asthma inflammation to treatment targets.

Announcer:
The current biologic therapies for asthma target type 2 inflammation dupilumab is a monoclonal antibody that binds IL-4 receptor alpha, which is the shared receptor for IL-4 and IL-13. By blocking this shared receptor, dupilumab blocks IL-4 and IL-13 mediated inflammation including production of IgE and exhaled nitric oxide, as well as trafficking of eosinophils. It is approved for eosinophilic and steroid-dependent asthma, as well as atopic dermatitis and chronic rhinosinusitis with nasal polyps. There were three biologic agents that block the IL-5 pathway and that are approved for severe asthma with eosinophilia. Mepolizumab and reslizumab are monoclonal antibodies against IL-5, whereas benralizumab is a monoclonal antibody against the IL-5 receptor. All three of these prevent eosinophil proliferation and activation. Mepolizumab is approved for eosinophilic asthma, chronic rhinosinusitis with nasal polyps, eosinophilic granulomatosis with polyangiitis, and hyper eosinophilic syndrome. Reslizumab and benralizumab are approved for eosinophilic asthma. Omalizumab is a monoclonal antibody that targets IgE. It is approved for allergic asthma, chronic idiopathic urticaria and nasal polyps. Emerging therapies include tezepelumab, a monoclonal antibody targeting TSLP, one of the key epithelial alarmins. Therapies targeting another epithelial alarmin IL-33 and its receptor are currently under active investigation.

Dr. Wechsler:
In sum, what we have shown today is that there are several current therapies, several biologic therapies that can have a significant impact on management of asthma. Anti-IgE therapy with omalizumab, anti-IL-5 therapies including mepolizumab, reslizumab, and benralizumab, an anti-IL-4 receptor alpha therapy that also blocks IL-13 in the form of dupilumab. I'm also excited about a variety of different emerging therapies, therapies that block TSLP including tezepelumab, and therapies that block IL-33 including astegolimab

and itepekimab. More data are sure to emerge in the coming years. These are really exciting time for our patients with severe asthma.

Now, let's review a few cases of patients with severe asthma and let's decide how we'd approach the management of those patients.

The first case is a 29-year-old female with allergies since childhood. She had mild, intermittent asthma as a child, which was generally triggered by allergies. But now she's got severe, persistent asthma that's been worsening over the last 10 years. Her Asthma Control Test score now is 14 indicating that she's poorly controlled. She's had three hospitalizations as an adult, once in the ICU, again triggered by allergies, as well as once by a wildfire and she's also been triggered by poor air quality or viral infections. She reports having two to three oral steroid requiring exacerbations each year. Her current medications include a high dose of inhaled corticosteroid and long-acting beta agonist and she's also on a leukotriene receptor antagonist, and she takes albuterol on an as-needed basis. Laboratory testing was done and shows that her total IgE level was 273. She had an exhaled nitric oxide level that was elevated at 65. She had an absolute eosinophilic count of 500, and sputum cell counts demonstrated 8% eosinophils and 50% neutrophils.

Eileen, how do you characterize this patient and how would you approach this patient before we decide what would be the best therapeutic approach?

Dr. Wang:
Great question, Dr. Wechsler. So, she absolutely has an allergic phenotype. You can see she has childhood asthma with triggers of allergies, but she also has some elements of non-type 2, so the 50% neutrophils definitely catches my eye. You can see she's got a mixed inflammatory phenotype with an 8% yu- eosinophils in the sputum, too.

Dr. Wechsler:
And on top of that, she gets exacerbated not only by allergies, but also by irritants, including smoke and also viral infections. So, she's got a mix of different types of inflammatory stimuli that can result in exacerbating her asthma.

So, which of the following inflammatory molecules would you target to decrease exacerbations for this patient? Would you target IgE, IL-5, IL-4, or TSLP?

So, for this challenging patient, what therapeutic options would you consider? W- how would you target- which cytokines would you target in trying to prevent exacerbations for this patient?

Dr. Wang:
Great, Mike, so I don't think there's a single correct answer here. Anti-IgE therapy could be considered, given her allergic phenotype. She also demonstrates significant peripheral and sputum eosinophilia, so an anti-IL-5 or 5 receptor therapy could be considered. Also, with her allergic eosinophilic and elevated exhaled nitric oxide, you can think about targeting the IL-4 and IL-13 pathway. And lastly because she demonstrates both that type 2 and non-type 2 mixed endotype you can think about anti-TSLP.

Dr. Wechsler:
Yeah, I agree. I think all those different therapeutic options area reasonable choices.

Dr. Wang:
Right.

Dr. Wechsler:
And none, none of them will probably be perfect. We know that all of the different monoclonals that we have, none of them completely obliterates exacerbations. They all reduce exacerbations somewhere between 50 to 60 and sometimes as much as 70%. So, I think all the answers are correct here. You might consider t- anti-TSLP for this patient only because it works a bit more broadly. It will prevent downstream up-regulation of the type 2 cytokines, IL-4, 5, and 13 and it may play some other role in terms of preventing some non-type 2 manifestations, as you mentioned. So, it might prevent some of the irritant effects and some of the viral mediated symptoms. I agree with you, however, all of these options would be reasonable choices for our patients.

Great. So, let's go onto another case. Eileen, do you want to present this one?

Dr. Wang:
So, for case number two, we have a 44-year-old man with daily asthma symptoms. He has a past history of eosinophilic asthma, no history of allergies, but he's having four exacerbations per year and his FEV1 is only 66% of predicted. In terms of his medications, he's currently on a high-dose combination inhaled corticosteroid and long-acting beta agonist. He was started on mepolizumab and he improved, but he is still having two exacerbations per year which is down from four and symptoms three to four days per week requiring rescue inhaler use. In terms of his testing, he's had total serum IgE, which is 55, and absolute eosinophilic counts of 80 while on mepolizumab, exhaled nitric oxide of 36 parts per billion and his ACT score is only 16. His sputum cell count was not evaluated.

So, our question is, targeting which of the following is most likely to benefit this patient? Continuing targeting IL-5, switch to target IL-4 and IL-13? Switch to target IgE? Switch to target TSLP? Switch to target IL-5 receptor alpha? Switch to target IL-4 and IL-13 or switch to target TSLP? And lastly, switch to target IgE? Or switch to target IL-5 receptor alpha?

Dr. Wechsler:
Lots of options there.

Dr. Wang:
Lots of options there.

Dr. Wechsler:
I think that this is the, kind of, patient who has been on anti-IL-5 therapy so the likelihood that he's gonna respond to continuing IL-5 therapy or even obliterating eosinophils further with anti-IL-5 receptor alpha therapy is unlikely to be helpful.

Furthermore, there's no history of allergies and their IgE level is relatively low, so I think targeting IgE is probably not gonna be too helpful.

Dr. Wang:
Agreed.

Dr. Wechsler:
So then, we're left with deciding between targeting IL-4 and IL-13, targeting TSLP, or either one of those, and I think, again, I don't think you can go wrong with either of those different options. In this patient, the exhaled nitric oxide's a little bit elevated at 36 parts per billion, so that would suggest, in combination with the fact that he had a history of eosinophilic asthma, that dupilumab may be helpful. On the other hand, targeting TSLP, which is upstream of the IL-4, 5, and 13 may be helpful, as well, and could also be a reasonable option for this type of patient. These kinds of patients seem to do well in the phase 3 tezepelumab study. And so I think using either dupilumab or anti-TSLP therapy with with tezepelumab would be a reasonable option.

Dr. Wang:
I think that this case does demonstrate that it might be helpful to maybe get those sputum cell counts to be able to see if there is some evidence of neutrophilic inflammation. But I agree, not exemplifying a strong allergic phenotype there. Already been tried to target that eosinophilic pathway with some benefit, but incomplete, and so going upstream for an anti-TSLP or switching to target the IL-4 and 13 pathway are completely reasonable.

Dr. Wechsler:
OK. well, let's move on to case number three. This is a 51 -year-old obese female who was diagnosed with asthma at age 34. She was initially having three to four steroid-requiring exacerbations per year and then she was finally started on daily oral corticosteroids a year ago. She's still having daily symptoms despite that and two to three exacerbations per year requiring escalation of her oral corticosteroid dosing. Mepolizumab was started but recently discontinued as it wasn't really helpful for her.

So, what is she on now? She's taking a high-dose inhaled corticosteroid long-acting beta agonist, she's taking a long-acting muscarinic agent, she's on 10 mg of prednisone a day, and she takes albuterol on an as-needed basis. In review of her testing, her total Ig level is 33, she has a low eosinophilic count after taking the apolizumab of 100 cells per microliter. Her exhaled nitric oxide level is low at 15 parts per billion, but she's poorly-controlled with an Asthma Control Test score of 14. And her sputum cell count showed very few cells with no specific cell type predominance. So, which of the following would be a possible next step in the management of this patient? Would you start omalizumab? Start dupilumab? Consider tezepelumab? Evaluate for bronchial thermoplasty? Or switch to a different anti-IL-5 therapy such as benralizumab or reslizumab?

Eileen, how would you approach this patient?

Dr. Wang:
So, this is a complex patient. Granted that her biomarkers while she's on oral corticosteroid therapy could be suppressed, but right now she's not demonstrating much of a type 2 endotype. She has low exhaled nitric oxide. Her absolute eosinophilic count is only 100 her, and her sputum cell count doesn't show much eosinophils or neutrophils, so she more of a paucigranulocytic phenotype while on prednisone therapy. As a result, I probably would lean away from anti-IgE therapy. In terms of dupilumab for anti-IL-4 and 13 targeted therapy, it is indicated for chronic corticosteroid-dependent asthma, but again, she's not really showing me too much of that type 2 endotype.

In terms of tezepelumab, for an anti-TSLP, it is upstream, so there could be some potential benefit but there have not been significant data supporting its use an oral corticosteroid therapy. In terms of Bronchial thermoplasty and azithromycin, that may be good

possibilities here. I'm not leaning so strongly towards switching to a different anti-IL-5 therapy or a 5 receptor therapy such as benralizumab or reslizumab given the lack of evidence for that eosinophil-like type 2 inflammatory pattern.

Dr. Wechsler:
Yeah, I agree with you. I think again this is another case where we have a lot of different options.

Dr. Wang:
Right?

Dr. Wechsler:
But there isn't a clear-cut choice for what to do in a patient who is oral corticosteroid dependent. The data for omalizumab anti-IgE therapy in- in steroid-dependent patients is poor and switching to a different anti-IL-5 therapy is unlikely to yield a significant benefit. And so, we're left with a few different options. The dupilumab is clearly indicated for oral steroid dependent patients so that might be a good choice, although as you mentioned, there isn't a lo- a strong signal for type 2 inflammation in this patient. And the tezepelumab data from the source study suggested that it wasn't that much better than placebo for these kinds of patients. Bronchial thermoplasty and azithromycin could be good options and I think you could go with either one. Azithromycin is certainly a less expensive, easier to take and easier to prescribe and so that might be a good choice, as well.

So, I think I would f- consider either dupilumab or tezepelumab and probably give azithromycin as well, while thinking about bronchial thermoplasty and the challenges of getting that approved.

Dr. Wang:
Correct. And one thing I would add is if you're able to wean this patient off of her prednisone therapy to see if sh- if it unmasks an inflammatory phenotype, that sometimes can be helpful, too.

Dr. Wechsler:
Exactly. Great idea.

How 'bout the fourth case?

Dr. Wang:
Alright, so for our fourth case, we have a 37-year-old man. He's diagnosed with asthma at the age of 28, so adult onset. He's had three to four steroid-requiring exacerbations per year, and he's still having daily symptoms. His medications include high-dose inhaled corticosteroid long-acting beta agonist maintenance and reliever therapy and a long-acting anti-muscarinic. In terms of testing, he's had total serum IgE of 25, so not significantly elevated. His absolute eosinophil count is 90 cells per microliter, so not very elevated. His exhaled nitric oxide is only 12 part per billion, and his ACT score is 14. So, which of the following would be a possible next step in management? Perform bronchoscopy? Do an extensive GI workup? Evaluate for bronchial thermoplasty? Or evaluate for anti-TSLP?

Mike, what would you choose?

Dr. Wechsler:
This seems like a non-type 2 patient. This person t- isn't on corticosteroids and he has not been on a prior biologic. And so, looking at the biomarkers, it seems as if the IgE level is low, the eosinophil count is low, the exhaled nitric oxide level is low. So, either this patient has a non-type 2 endotype of asthma, or this patient may not even have asthma. And so, it's important to evaluate that patient and see what else could be going on. For these patients, I like to do an extensive workup before considering what therapy to do next. I would generally characterize the patients, make sure that they have bronchodilator reversibility, confirm that they have asthma, either with that or with air- evaluating airway hyperresponsiveness, like with a methacholine challenge. And then I'd probably still do an extensive GI workup, or at least take a history to see if there's significant reflux or aspiration.

In terms of the therapeutic options that we have listed here evaluating for bronchial thermoplasty is reasonable. It's been shown to reduce exacerbations by as much as 50% in patients with severe asthma and so it could be a good option, particularly for patients with non-type 2 asthma. But I think again here, we might also consider anti-TSLP therapy with tezepelumab. This patient has non-type 2 asthma, and I think in these kinds of patients we need to be cautious. We need to evaluate the data with tezepelumab, which seems to be effective in patients with non-eosinophilic asthma in addition to eosinophilic asthma. So, I think anti-TSLP therapy would be a good option here, as well. So, I think this is w- one of those cases gain where I'd probably do all of these things. I would do an extensive workup and then I would probably choose between anti-TSLP and bronchial thermoplasty as my primary treatment strategy for this patient with non-type 2 disease.

Dr. Wang:
I think you bring up some great points. One, to confirm the diagnosis, two to always evaluate for comorbidities even if it's been done

prior, things can change so th- doing the GI workup, chronic rhinosinusitis chronic aspiration, there can be a lot of contributing factors there. And then also i- evaluating adherence and technique of inhalers and then as you said, bronchial thermoplasty, anti-TSLP, there are some options here that weren't available before and also bronchial thermoplasty's been available for some time and in the right population, there have been some improvements seen. So-

Dr. Wechsler:
And then-

Dr. Wang:
Yeah.

Dr. Wechsler:
Another, another advantage of bronchoscopy is you can evaluate the vocal chords and you can also evaluated the inflammatory milieux and also look for structural changes in the airways to see if there's any kinds of strictures or if there is tracheal bronchial malacia and so that might be beneficial, as well.

Dr. Wang:
Great.

Dr. Wechsler:
Thank you for joining us for this presentation. Please complete the post-test and evaluation to earn your CME certificate.

Announcer:
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