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

Announcer Open:
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Dr. Doyle:
Hello, and welcome to another CHEST webinar. Today we will be talking about Targeting TSLP in Severe Asthma: A Case-Based Exploration for the Pulmonologist. My name is Dr. Stephen Doyle. And today we have Dr. Navitha Ramesh and Dr. Sandhya Khurana joining me.

So our learning objectives today are going to be to evaluate the impact of TSLP on asthma, clinical manifestations, symptomatology, and disease course. We'll also be reviewing the evolving and expanding evidentiary base for monoclonal antibodies in severe asthma treatment calculus. And finally, we will design an individualized evidence-based treatment plan for severe asthma that incorporates both the patient voice and empower shared decision-making.

As I said, I'm Dr. Steven Doyle. I'm an Assistant Professor of Medicine and the Associate Program Director of our Pulmonary Critical Care Fellowship at Corewell Health West at Michigan State University College of Human Medicine, Grand Rapids, Michigan.

So to get started, asthma is a chronic disease state characterized by a history of respiratory symptoms, such as wheezing, shortness of breath, chest tightness that have two main components. They vary in time and intensity, and then they have variable inspiratory flow limitation. It's estimated that approximately 262 million people were affected with asthma in 2019 worldwide, that led to approximately 455,000 deaths worldwide. In the United States, this approximately affects 25 million people in 2021, which correlates to about 7.7% of the population. With this many people, asthma can clearly be a large healthcare burden. And it's projected that over the next 20 years, there'll be $963.56 million U.S. dollars, both direct and indirect costs, that will be incurred because of asthma. In addition, it'll lead to 15.46 million quality adjusted years lost.

So the prevalence of asthma has been increasing over the past couple of decades. Back in the early 1980s, we had a prevalence of around 2%, 2 to 3%, that increased closer to kind of around 5.5-6% in 1996. Since then, our current asthma prevalence has increased, again, up to where it is right now, just at about under 8% here in 2021. This has also led to an increase in healthcare utilization and ER visits. Even though there has been a slight downtrend over the past couple of years, we're still numbering over 62.6 ER visits per 10,000 people. Well, that was back in 2010, and now it's down to 46.5 per 10,000 in 2019. Our hospitalization rates have decreased as well, and those are running at about 5.2 per 10,000 people. So we have seen a decrease in both ER visits and asthma hospitalization over the past few years, but it's still a very large healthcare burden.

So with asthma, it's such a multifactorial disease, that we always want to talk about the asthmatic cascade. These are a group of cytokines and immunological cells that interact that cause different symptoms throughout the process. And there's 4 major components that can be attributed to asthma; we can have an allergic eosinophilic type that you're going to see on the left side of the screen, we can have a non-allergic eosinophil type, we can have a non-eosinophilic type, that's really our non T2-driven inflammation, and our prior

ones where T2-driven inflammation, and then you can get structural changes related to this chronic disease process.

So starting, we'll look at the allergic eosinophilic pathway. So in this process, there's some kind of allergens that affect the respiratory tract that you inhale. It's going to go to these respiratory epithelial cells and get taken up by the epithelium. There's multiple mechanisms at play that will lead to asthma symptoms happening. So one of the first things is alarmins get released such as TSLP, which that itself can go and lead to dendritic cells that will help CD4-naive T cells alternately differentiate to these naive T cells to become Th2 cells. The Th2 cells can then lead to the production of IL-4, IL-13, and IL-5, which can ultimately lead to B cells leading to IgE switching, degranulation of mast cells, airway eosinophilia, mucus hypersecretion, and smooth muscle contraction, leading to airway hyperresponsiveness, and is one of the classical findings in asthma.

Next, we can have more of a non-allergic eosinophilic pathway, and this can be produced by viruses, bacteria, pollutants, such as cigarette smoke, or any kind of inhaled toxin that you're going to have. These can also lead to alarmins being released from the respiratory epithelial cells such as TSLP, IL-33, IL-25, which then they can activate the group 2 innate lymphoid cells, which can lead to the production of both IL-5 which can attract eosinophils and lead to increased production and also lead to mucus hypersecretion and airway hyperresponsiveness.

Now, moving more towards the non-eosinophilic pathways, these are our non-T2 asthmatics. We can have exposure to some kind of environmental insult as well. Ultimately, this is going to lead an airway neutrophilia. This mechanism is still being elucidated in labs, but it is thought to be that it's related to TSLP being released from the respiratory epithelial cells again, that is activating the dendritic cells, which then will buy into naive T cells, leading to a Th17 cell differentiation, which ultimately this will lead to IL-17A production, which can stimulate the bronchial epithelial cells to produce neutrophilia-promoting cytokines such as CXCL8 or GM-CSF, which will lead to neutrophil production and then airway remodeling by altering the functions of airway smooth muscle self.

Finally, something that happens in our asthmatics are these structural changes that we see. So these mechanisms can include smooth airway muscle cell migration, that mediates crosstalk between these airway smooth muscle cells and mast cells. Both of these cells can produce TSLP and inflammatory cytokines, such as CCL11, CXCL18, and IL-6. And it can lead to structural changes that develop from that. TSLP can also stimulate human lung fibroblast cells that lead to the production of collagen, and promote airway remodeling.

So now that we've talked a little bit about what the cascade looks like, and what is happening at a cytokine level from a physiological standpoint, what do we mean when we talk about severe asthma? So in 2014, the ERS and ATS developed a severe asthma definition for this chronic disease. What they classified it as is someone that's requiring treatment per GINA guidelines steps 4 or 5 for the prior year. This is generally going to be a medium to high-dose inhaled corticosteroid and a long-acting beta agonist plus possibly a secondary controller medicine. They're going to either require systemic corticosteroids for more than 50% of the prior year to prevent worsening, and despite all this, symptoms are uncontrolled, despite these above therapies.

But if we're going to classify someone as severe asthma, we need to make sure that it's different than just uncontrolled asthma. So the way that we differentiate from uncontrolled asthma is by looking at the following. Are there poor symptom control based off the Asthma Control Questionnaire or the Asthma Control Test? Do they have frequent exacerbations, 2 or more bursts of systemic corticosteroids in the prior year? Or is this a more serious exacerbation that requires a hospitalization, such as an ICU stay or mechanical ventilation? And then despite all the above therapies, are their air flow limitations after the appropriate bronchodilator withhold an FEV1 of less than 80% still? And if we tried to taper any of these above treatments that we talked about in GINA 4 or 5 steps, there is worsening of the symptoms.

So now that we know what severe asthma is, let's talk a little bit about what our goals are in controlling asthma. So we want to achieve control and we also want to reduce for future risks. So when we're looking to achieve current control, that's really looking to address our symptoms. How are people feeling? Look at their reliever medication use. Are they constantly having to reach for their rescue inhaler to provide some kind of reliever support? Are they able to function at a normal level and have their normal activity? And then is their lung function being maintained? And our goal is to reduce future risk, is really to try to prevent any instability or worsening, protect the lung function, minimize any medication adverse effects, and ultimately minimize exacerbations that lead to corticosteroid use, hospitalizations, ICU stays in patients.

So when we're evaluating asthma, it's extremely important that, one, we make sure that we have the right diagnosis, especially if someone's not responding appropriately to therapy, as you might expect them to. It's important to step back and say, 'Hey, do I have the right diagnosis? Is this actually a severe asthma that I'm treating?' Second is to look at the guidelines, look at the GINA guidelines, step-up therapy as necessary, and based off symptoms is the patient on an appropriate level of therapy? Third, check adherence. Have the patient demonstrate what they're doing, make sure that the correct inhaler technique is going on. Because if they're improperly using the inhalers, they're not going to be getting the adequate response. So teaching and making sure that they're adhering and having the correct technique is paramount. Making sure comorbidities are controlled, such as obesity, GERD, sinus disease, making sure things

that we know worsen asthma are controlled. And then finally, especially in the allergic T2-driven pathway, make sure that our triggers are identified and addressed. We want to make sure if there is an allergic exposure, there is something they're constantly being exposed to, are we at a way that we can minimize that or optimize that as best as we can?

So when we look at what we consider uncontrolled asthma, there's the uncontrolled asthma, difficult asthma, and then the severe refractory asthma. Generally our uncontrolled asthma has a prevalence of about 50%. We stepped up the controller medicines, we can get to a difficult controlled asthma of roughly around 15 to 20%. And once we've ruled out that there's an incorrect diagnosis, make sure it is asthma that we're actually treating, address adherence, and control these comorbidities as much as we can, and eliminate your triggers. That's when we actually are talking about the severe refractory asthma, which at that point, is going to be less than 5%.

So next, I would like to invite Dr. Navitha Ramesh to talk to us more about a T2 asthma case-based discussion.

Dr. Ramesh:
Hello, everyone. My name is Navitha Ramesh. I am a Pulmonary Critical Care Physician at UPMC Harrisburg in Harrisburg, Pennsylvania. Today I'm going to discuss T2 asthma, a case-based discussion.

So we have a patient Miss B. She is a 33-year-old female seen – she is being seen in the outpatient clinic. She's just moved to the area. She was diagnosed with asthma as a child. However, she's been symptom free from age 18 up until now. She has received 2 courses of prednisone over the past month for episodes of cough, chest tightness on exertion, which improve with as-needed albuterol. The review of systems include rhinitis, nasal congestion, postnasal drip, occasional early morning nonproductive cough, and wheezing, and she does endorse some snoring as well. Review of system was negative for gastroesophageal reflux, leg swelling, or chest pain. Her asthma triggers include cold weather and exercise. She has not had any ED visits or hospitalization up until now. Her past medical history includes allergic rhinitis and acid reflux. Her past surgical history reveals nasal polypectomy.

Her family history is significant for her mother and younger sister with asthma. Her social history reveals 1-pack-year tobacco use at around the age of 22. And there's no vaping history. Her medications include budesonide formoterol 80/4.5 mcg 2 puffs twice a day, montelukast, albuterol as needed, loratadine, and ranitidine. On examination, she is saturating 98% on ambient air. Her BMI is 25. She appears comfortable. Significant positives include positive nasal turbinate hypertrophy and maxillary sinus tenderness. Her lung evaluation revealed diminished air movement bilaterally with occasional mild end expiratory wheezing and she did not have any lower extremity edema. Her Asthma Control Test score in the clinic was 24. The spirometry done in the office revealed and FEV1/FVC of 81, FEV1 of 3.17 liters. Her total lung capacity was 75% predicted and DLCO was 112% predicted.

So looking at the GINA recommendations for patients with poorly controlled asthma on an inhaled corticosteroid and long-acting beta agonist, so our patient is right now either in step 4 or step 5. So in these situations, the recommendation is to increase the dose of ICS/LABA, to change the patient to a high dose ICS/LABA. Tiotropium could be used as well. And so this is what we did with our patient. So Miss B again, she's a 33-year-old female with a BMI of 25. In the office, her FeNO testing revealed exhaled nitric oxide level of 56 parts per billion. We evaluated her comorbidities and managed them in an optimal manner. Tiotropium was added as mentioned before, and her inhaled corticosteroid LABA dose was increased to 160/4.5 for 2 puff twice a day. Inhaler technique was reviewed and feedback was given. Trigger avoidance was stressed. And patient was set up for a follow-up visit.

So the patient returned 3 months later for her 3-month follow-up visit. And she had mentioned she's had 3 exacerbations since our last visit leading to ED visits, needing systemic steroids. She did endorse good inhaler adherence, confirmed trigger avoidance, and other comorbidities were actively and optimally being managed. In the office, her exhaled nitric oxide level again was increased to 71 parts per billion increased from 56 from 3 months ago. She had bloodwork with CBC and differential that showed an absolute eosinophil count of 540. Her blood panel for allergies was negative.

So now referring back to the personalized asthma management based on the GINA recommendations, we assessed our patient, we adjusted the medications, and now we are reviewing the patient's symptoms. And we did follow the path up until step 5. So what's next?

So this is a point where we would refer the patient for phenotype assessment and then consider after we've added her inhaled corticosteroid formoterol combination, we would consider a biologic therapy in this patient. So before we move on to the details about biologic, it's important to emphasize that heterogeneity in asthma is not a new concept. This paper titled: The Heterogeneity of Asthmatic Patients an Individualized Approach to Diagnosis and Treatment. This paper was initially published in 1976. Now, today, as we know, asthma has different inflammatory subtypes, which are based off of airway inflammation. The phenotypes of asthma could be eosinophilic asthma, neutrophilic, paucigranulocytic, or mixed eosinophilic and neutrophilic phenotypes. When we endotype our asthma patients, there's a type 2 or a T2-high endotype and non type 2 or a T2-low endotype. Another way to look at the endotypes, the T2-high is the allergic, it could be allergic or eosinophilic which include elevated biomarkers, such as blood eosinophils, sputum, or BAL eosinophils, exhaled nitric oxide, increased serum IgE, increased IL-4, IL-5, and interleukin-13 as well. The T2-low endotype could have

2 phenotypes, could be neutrophilic or paucigranulocytic. And different kinds of inflammatory cytokines are elevated in this condition, or the patient could have a mixed endotype and a mixed granulocytic phenotype, which has both increased neutrophils and eosinophils within the lungs.

This slide reiterates what was discussed before. It compares the T2-high and the T2-low inflammatory response in asthma. So based on the phenotype of neutrophilic inflammation or eosinophilic inflammation, patients are classified into T2-low asthma or T2-high asthma. This slide was discussed by Dr. Doyle previously, looking at the asthmatic cascade. It is important to understand the cascade because this is - from here is where we talk about the biologic targets in asthma. So, as you see here, TSLP, or thymic stromal lymphopoietin, it's an alarmin, it's secreted by the epithelial cells right at the entry into the airways, and it acts on top of the inflammatory cascade, and it regulates several downstream cytokine effects within the lungs. One of the biologics, omalizumab, inhibits IgE. Mepolizumab inhibits anti-IL-5. Reslizumab is anti-IL-5 as well. Benralizumab is anti-IL-5 receptor alpha antibody. Dupilumab is anti-IL-4 alpha, which targets both IL-13 and IL-4. And tezepelumab is anti-TSLP monoclonal antibody. So knowing that, tezepelumab, as you see, acts on TSLP. Again, it's on top of the inflammatory cascade and hence inhibits the downstream effects.

This slide here gives us a list of the approved biologic agents for severe asthma and the targets as well. The most recent one is tezepelumab which was initially approved by FDA in December 2021, indicated for those with asthma over age 12 years who have severe asthma.

So when considering a biologic therapy for a patient with severe asthma, there are multiple options. When would you consider anti-IgE? And what are the predictors? When would you consider an anti-IL-5, an anti-IL-4 receptor alpha, or anti-TSLP? So, this slide gives us - this is from the GINA guidelines, it gives us a recommendation as to the pathway to follow when considering biologic therapy in patients with asthma.

Coming back to our patient, Miss B, she's again 33-year-old female with T2 asthma. She has high FeNO, high eosinophiles, and negative allergen testing. The biologic treatments per our previous slide, the biologic treatments that are available for her are anti-IL-5, anti-IL-4/13, and TSLP blockade. So this patient was started on anti-IL-5 antibody initially; however, she had 2 more exacerbations at 6-month follow-up.

So upon discussing with the patient, again, optimizing all the other comorbidities and reviewing all the inhaler techniques, a shared decision was made with the patient, and the patient was switched to tezepelumab. This brings us to what is tezepelumab and what are the studies that have been done to look at tezepelumab in adult and adolescents with severe uncontrolled asthma. So this study, initially published in *New England Journal* had 584 patients with severe uncontrolled asthma and were started on tezepelumab versus placebo. And the study revealed that tezepelumab reduced the blood eosinophil count, FeNO levels, and serum IgE levels in these patients. So phase 2b clinical trial where patients were divided into 3 groups; low-dose tezepelumab, medium dose tezepelumab, and high dose. And all these groups reduced exacerbation across all the patient groups by 70%. More patients in the tezepelumab group achieved well-controlled asthma and as well as partially controlled asthma at 52 weeks when compared to placebo.

This was followed by another study looking at tezepelumab in adults and adolescents with severe uncontrolled asthma, looking at 1,000 patients - over 1,000 patients, placebo versus tezepelumab. And it showed a 56% reduction in overall asthma exacerbations with tezepelumab use. This study looks at the change in the baseline prebronchodilator FEV1, Asthma Control Questionnaire 6, and Asthma Quality of Life Questionnaire in the same patients who were on tezepelumab versus placebo. And there's significant improvement in all 3 characteristics in the tezepelumab group.

In both the PATHWAY and NAVIGATOR trials, which were both 52 weeks, tezepelumab trials looking at the annualized asthma exacerbation rate, both studies showed that using this medication compared to placebo across the phenotypes in a broad population of patients with severe asthma and it showed favorable results with tezepelumab use. So the annualized - the asthma - annualized asthma exacerbation rate over 52 weeks in this study was consistently lower in the tezepelumab group than in the placebo group across the various biomarker spectrum. So regardless of the eosinophil counts, the FeNO counts, or the IgE level, tezepelumab did show significant improvement compared to placebo.

Another slide looking at that is this, the phase 3 NAVIGATOR study, showed reduction in all 3 of the biomarkers which is blood eosinophils, FeNO, and IgE over the 52-week period. And it's interesting to know that within 2 weeks of starting tezepelumab, there is a change in the eosinophil count and the FeNO level as well and this change is significant over the 52 – it remains consistent over the 52-week period.

So both the NAVIGATOR and the PATHWAY trial showed reduction in interleukin-5 and interleukin-13 levels with tezepelumab. In patients with symptomatic asthma, there was reduction in IL-5. This was shown by a higher dose on intravenous tezepelumab 700-milligram dose in the phase 2 UPSTREAM study as well.

So based on what we know so far, tezepelumab reduces the blood eosinophils levels, airway eosinophils count, FeNO levels, and IgE levels in patients with moderate to severe and severe uncontrolled asthma.

Now coming back to my patient, Miss B, again, 33-year-old female with T2 asthma. She initially had high FeNO, high eosinophil, and negative allergen testing. She was switched to tezepelumab from an anti-IL-5, and at 3-month follow-up, she remained exacerbation free. So the summary for T2 asthma, T2 asthma can be allergic or non-allergic eosinophilic asthma, there are multiple endotypes, and each of those has multiple targets. The biomarkers may overlap. And all available allergy therapies are effective, biologic therapies especially, are effective in T2 asthma. And the selection should be based on the biomarkers, looking at the patient's phenotype and endotype, the comorbidities, the patient preference, as well as cost.

With this, I would like for Dr. Khurana to continue path discussion.

Dr. Khurana:
Thank you, Dr. Ramesh. That was an excellent overview of management of type 2 asthma. I'm Sandhya Khurana at the University of Rochester, Professor of Medicine and Director of the Asthma Center. And my task over the next several minutes is to review management of non type 2 asthma.

So this is a patient that presented with symptoms of cough and dyspnea for 6 months, 52 years old, who does not have history of childhood asthma. Her symptoms started after a respiratory infection. She endorses frequent wheezing, chest tightness, she's using her albuterol 2 to 3 times a week as rescue inhaler, and main triggers are exercise and exposure to smoke. But several of these symptoms are occurring spontaneously as well. And in the last 6 months, she has experienced 2 exacerbations requiring oral steroids, and one of them resulted in an ED visit. In terms of comorbidities, she has gastroesophageal reflux disease, but her symptoms are controlled on a proton pump inhibitor therapy. She also has obstructive sleep apnea diagnosed and has tried to use CPAP, but like many of our patients, has not been able to tolerate it. There's no childhood history of any atopic disease including asthma or allergies. She's a lifelong nonsmoker, works as an elementary school teacher. No pets at home. No family history of asthma or allergies. Her current medications, she's currently on a combination ICS/LABA, the ones she's currently using as fluticasone and salmeterol high dose 500/50 mcg, 1 inhalation twice daily. It's a dry powder inhaler. She's also taking a leukotriene modifier, montelukast 10 mg every night, omeprazole in the morning as I mentioned, and albuterol as needed. On exam, she appears comfortable. Oxygen saturations are normal on room air. Her BMI is elevated at 34. Nasal exam does not reveal any erythema or nasal polyps. On auscultation, her lungs have decreased air movement bilaterally but otherwise clear to auscultation. And she has no appreciable edema in her lower extremities.

This is her spirometry from that visit. As you can see, she has a prebronchodilator and a postbronchodilator, so spirometry with bronchodilator challenge that was performed. And her FEV1 is reduced at below the lower limit of normal with a Z score of -2.43. So she has a moderately - mildly reduced airflow obstruction with a reduced FEV1/FVC ratio. But after bronchodilator challenge, this improves significantly, and meets criteria for a bronchodilator response with normalization of her postbronchodilator spirometry. Also, you can see this here in the flow volume loop and the volume time curve, the separation pre and postbronchodilator. So based on this, we assess that she had evidence of obstructive impairment with a positive bronchodilator response.

So as Dr. Ramesh alluded to this GINA stepwise therapy, at this point, she was already on high-dose inhaled steroids. She also was on a leukotriene modifier and was using a short-acting beta agonist, and we started looking at step 5 in terms of what else can be done. And this is where we started talking about phenotyping her. So based on her evaluation so far, as you make that, you know, comorbidities are best optimized as possible, she's adherent to her medications, there are no identifiable triggers, we went ahead and checked biomarkers. And these are the 3 biomarkers that we would usually check out when clinically phenotyping our patients. Her exhaled nitric oxide level, which is a measure of interleukin-13 activity was 13 parts per billion. So that's low, it's less than 25 parts per billion, likely low also because she's on high dose of inhaled steroids. Her blood eosinophil count was also low at 100 cells per microliter, and her IgE level, total serum IgE level was 35 with negative allergen skin testing.

So, you know, we think that this patient has non type 2 asthma. And we used to think that non type 2 asthma is fairly common and makes up for about 30 to 50% of patients with asthma. But there's been recent advances in understanding this particular phenotype. And this is a graph from the International Severe Asthma Registry that was published in 2021, where this large cohort of patients with severe asthma were phenotype based on these 3 biomarkers. And as you can see, there was significant overlap. And what they found was that only 12% of patients in this large cohort of over 1,000 participants had truly negative triple-negative biomarkers. So we believe now that non type 2 asthma is not as common as we used to think it is.

The management of non type 2 asthma is really challenging. And it's for many reasons, you know, while type 2 asthma has been really well characterized, and mechanisms are really well understood, non type 2 asthma, there's no clear definition. And recognition is not based on a positive biomarker, but you have to have negative biomarkers, you have to have - they have to have FeNO, IgE, negative

allergen testing, and no evidence of eosinophilia. And as you know, these are very variable biomarkers, they vary over time, they're affected by anti-inflammatory therapy, and therefore multiple measures are needed before we can truly ascertain that a patient has non type 2 asthma.

With a non type 2 asthma, multiple endotypes exist. We've already heard about neutrophilic and paucigranulocytic asthma, and the multiple inflammatory pathways that lead to this. And they tend to be treatment responses, especially response to anti-inflammatory therapy is poor, including to corticosteroids. There really are no targeted therapies or were no targeted therapies available, and this remains an area of unmet need. And initial approach to management for type 2 and non type 2 asthma is really very similar. We've already talked about it earlier in the podcast - in the webinar.

What are the additional considerations when I'm evaluating somebody with possible non type 2 asthma? As I said, always look for intermittent eosinophilia, effective high doses of oral or inhaled steroids masking type 2 inflammation. Sometimes we can capture blood eosinophilia only when they're having an exacerbation. So if that's somebody who calls with an exacerbation, I try to see if we can get – check their blood eosinophil count before they start their oral steroids. Sometimes, the airway inflammation is not always measurable in the blood. So some of these patients may need sputum induction if it's available at your center. And then within the larger umbrella for non type 2 asthma, we have to consider what is the phenotype? For example, obesity-associated non type 2 asthma responds really nicely to weight loss.

So what are the advanced therapies I consider in a patient with non type 2 asthma? Long-acting muscarinic antagonists, there's increasing data with this. Macrolides, which I'll review briefly in the next couple of slides. And tezepelumab is the only asthma biologic that is approved for use in severe asthma regardless of phenotype. Bronchial thermoplasty, I'm not going to discuss that too much. It's really no longer being recommended by guidelines outside of a registry or a clinical trial. And this is data from 4 for phase 3 clinical trials, including over 900 participants with severe asthma aware they showed that the effect is maintained across increasing eosinophil count and IgE levels. So even in the low spectrum, which the non type 2 asthma would fall here, tiotropium or LAMA was effective.

The data for azithromycin in use in moderate to severe asthma comes from this large randomized controlled study, the AMAZES study. This was an Australian study of over 400 participants who had persistent symptoms despite use of ICS/LABA, and they were randomized to azithromycin 500 mg 3 times a week, compared to placebo, and studied over 48 weeks. And what they found was there was overall significant decrease in the annual asthma exacerbation rate by about 41%. And then when subgroup analysis was performed, azithromycin seem to perform well and had significant efficacy, both in eosinophilic and non-eosinophilic asthma. So this would be something to consider in our patients who have non type 2 asthma. Just keep in mind that these patients need their hearing monitored, QTC checked and monitored during study, and safety beyond 1 year is really not known or has not been documented.

And then let's talk about tezepelumab, which targets the epithelial cytokine, TSLP. We've already heard about the cascade and the inflammatory pathways by Dr. Doyle and Dr. Ramesh reviewed some of the clinical data. So I'll just briefly mention that this was the phase 2 study looking at - this was the dose-ranging study 210 mg, q4 weeks is what was finally approved by the U.S. FDA. And there was efficacy across the 3-doses study but when they looked at further subgroup analysis based on the type 2 status, tezepelumab seemed to perform compared to placebo, quite well, even in the low eosinophil, low FeNO, and low Th2 status.

Similarly, in this large phase 3 study that was the pivotal study leading to FDA approval, where there was significant improvement in exacerbations in the overall population. But again, a similar efficacy was seen even in patients who had low eosinophil count. And the subgroup analysis, again showed that there seemed to be a type 2 effect with increasing efficacy, with increasing eosinophil count and exhaled nitric oxide levels, but even then, patients who have low FeNO and low eos, tezepelumab was significantly better than placebo.

So this is the algorithm that I consider when I'm evaluating a patient with non type 2 asthma. The first question is, is that, as Dr. Doyle mentioned, you know, is it really asthma? Make sure that we are confirming objectively the diagnosis, look multiple times for evidence of type 2 inflammation. And then, you know, consider these therapies. Of course, the usual things that we do for all our patients are listed here in obesity, weight loss and better diet and exercise helps as well. And then now tezepelumab, this place was empty until 2021. And now we have one biologic therapy that's available.

So just to wrap up the non type 2 path, severe non type 2 asthma is less common than previously thought. There's really no agreed-upon definition, mechanisms need to be further elucidated. It's not as corticosteroids responsive, no positive biomarkers, multiple challenges in management of non type 2 asthma. And tezepelumab currently is the only biologic that's approved for use, regardless of type 2 status. Dupilumab can be considered in patients who are corticosteroid dependent, if eosinophilia cannot be confirmed, but it remains a type 2 a biologic. So this really remains an area of unmet need.

So I'm going to pass this back on to Dr. Doyle to wrap up the entire webinar. And thank you for your attention.

Dr. Doyle:

Well, thank you very much for that, Dr. Khurana and Dr. Ramesh, that was a great summary on both what is T2 and non T2 asthma and the challenges of managing both of those patient populations, and how we can use guidelines and these phenotypes that we're learning more and more about to provide the best care for our patients.

So in summary, asthma's prevalence is increasing over the previous decades, and it's still a large burden on our healthcare system, both in the United States and across the world. It really is important to differentiate uncontrolled asthma from those who truly have severe asthma, which as we discussed previously, is really less than 5% of asthmatics. As time goes on, our understanding is improving and evolving. The asthmatic cascade and treatments and phenotypic analysis is improving with that. It really is important to phenotype these patients and then ultimately direct treatment toward the biomarkers and cytokines that you're finding. Majority of the times, as Dr. Khurana said, it's going to be some kind of T2o asthma. And those are absolutely going to respond differently than our non T2 asthma patients. And the non T2 asthmas have much less treatment options compared to our T2 asthmatics. And as Dr. Khurana said, just 1 out of the 6 biologicals available are available in those non T2 asthmatics.

So, on behalf of Dr. Rames, Dr. Khurana, and myself, we'd like to thank you for joining us today on this webinar. And thank you to CHEST for allowing us to present this. Please visit chestnet.org for more educational events and opportunities. Thank you all.

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