Transcript Details
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Severe Asthma: An Exploratory Study on Mucus Plugging

Announcer:
Welcome to ReachMD. This medical industry feature, titled “Severe Asthma: An Exploratory Study on Mucus Plugging,” is sponsored by Amgen and AstraZeneca.

Here's your host, Dr Charles Turck.

Dr Turck:
This is ReachMD, and I’m Dr Charles Turck. Joining me today is Professor Arnaud Bourdin to discuss the role of mucus plugging in severe asthma, and review the clinical data and an exploratory study of a biologic therapy.

Professor Bourdin, welcome to the program.

Professor Bourdin:
Great to be here.

Dr Turck:
So, Professor Bourdin, would you mind kicking things off with some insight into what makes severe asthma challenging to treat?

Professor Bourdin:
Yes, that’s a great place to start because we now know that the complexities of severe asthma make it a diverse and unpredictable disease, with different triggers activating various pathways.[1,2,3] Patients with severe asthma can have multiple causes of inflammation, which can lead to overlapping or changing phenotypes.[4,5,6] As a result, treating this condition can be challenging.

In fact, approximately 60 percent of U.S. patients on treatment for severe asthma remain uncontrolled or partially controlled.[7] And as we know, uncontrolled asthma can lead to recurrent exacerbations, which is why having options is important to reduce attack risk and improve lung function and symptom control.[8,9]

Dr Turck:
With that context in mind, I’d like to turn our attention to mucus plugs. What do we know about their role in severe asthma?

Professor Bourdin:
The mucus plugs result from the production of pathologic mucus, which isn’t as easily cleared as typical mucus and can lead to airway obstruction.[10] These plugs have been found in patients with acute and chronic severe asthma and studies have shown that they may drive some of the lung function deficits seen in severe asthma.[10]

Now it’s important to note that the majority of severe asthma patients have been shown to have mucus plugs. In one study by the NIH-funded Severe Asthma Research Program, or SARP for short, 68 percent of severe asthma patients had mucus plugs compared to 40 percent of non-severe asthma patients.[11] Additionally, recent studies have determined that these mucus plugs can persist despite standard treatment and these persistent mucus plugs are associated with severe airflow limitation and more asthma exacerbations.[12]

We’ve also seen that sputum gene expression of interleukin-5, or IL-5, IL-13, and eosinophil levels are higher in patients with high mucus scores, pointing toward the type-2 inflammatory pathway as the origin of mucus plug pathology. And we now have a model, supported by data, which shows that the formation of mucus plugs is a result of the interaction between IL-5 activated eosinophils and IL-13 stimulated mucin.[10]

Dr Turck:
And as a follow-up to that, could you breakdown the mechanism of disease of mucus plugs in severe asthma?

Professor Bourdin:
Of course, and if we're going to be taking a look at their mechanism of disease, it's important that we take a step back from type-2 inflammation—which leads to mucus plug production—and begin at the top of the inflammatory cascade in severe asthma.[10]

The airway epithelium plays a critical role in asthma inflammation by acting as a physical barrier and environmental sensor.[13,14] Upon exposure to pathogens, allergens, pollutants, epithelial cells can induce airway inflammation and structural changes through the release of epithelial cytokines, known as alarmins.[13,15] Following epithelial damage or immune cell activation, alarmins can activate downstream innate and adaptive immune responses.[14,16]

In allergy-related type-2 inflammation, we have type-2 T helper cells, also called Th2 cells, which are joined by activated basophils. Together, they stimulate IL-4 and IL-13 release, which induces immunoglobulin E, or IgE, class-switching in B cells. Th2 also stimulates IL-5 production, which activates eosinophils, and—along with IL-13—activates mast cells. Meanwhile, type 2 innate lymphoid cells, or ILC2s for short, trigger the production of IL-5 and IL-13, resulting in eosinophil activation and non-allergic airway inflammation.[2,15,17-19]

So, with all that in mind, let's talk about TSLP, which stands for thymic stromal lymphopoietin. TSLP is an alarmin that drives Th2 responses indirectly through dendritic cells and T cells—and it's been shown to play a role in allergy and asthma pathophysiology.[14] The reason is that TSLP affects not only type-2 inflammation, but also type-2 independent pathways across allergic, eosinophilic, and smooth muscle-mediated components of asthma.[2,14]

On taking a closer look at the eosinophilic pathway, we find that TSLP is involved upstream from the release of IL-13 and IL-5—which as you'll remember, are the cytokines involved in the development of mucus plugs.[2] TSLP is positioned at the top of the inflammatory cascade, driving multiple inflammatory pathways that contribute to asthma-related airway inflammation and mucus plugging.[2,14,20]

Dr Turck:
Thank you for taking us through the inflammatory cascade, Professor Bourdin. So now I'd like to take a closer look at clinical data for the biologic TEZSPIRE, or tezepelumab-ekko.

Let's review the indication, usage, and some safety information.

Announcer:
INDICATION AND CONTRAINDICATION
TEZSPIRE is indicated for the add-on maintenance treatment of adult and pediatric patients aged 12 years and older with severe asthma.

TEZSPIRE is not indicated for the relief of acute bronchospasm or status asthmaticus.

TEZSPIRE is contraindicated in patients with a known hypersensitivity to tezepelumab-ekko or excipients.

Additional **IMPORTANT SAFETY INFORMATION** will be presented in this program.

Please stay tuned until the end of this program to hear the full Important Safety Information for TEZSPIRE.

Dr Turck:
So now that we've reviewed the clinical indication for TEZSPIRE, let's turn to the clinical data. Professor Bourdin, can you walk us through the evidence supporting the efficacy and safety profile of tezepelumab in severe asthma?

Professor Bourdin:
I'd be happy to.

Tezepelumab was studied in the PATHWAY and NAVIGATOR clinical trials, which included patients with multiple severe asthma phenotypes and biomarker profiles.[20-23] The PATHWAY and NAVIGATOR trials were conducted to assess the safety and efficacy of tezepelumab when added to standard of care for patients with severe, uncontrolled asthma. Over 1300 patients participated in the randomized, double-blind, and placebo-controlled trials, which lasted for 52 weeks. Throughout each study, patients continued their background asthma therapy, which included medium- or high-dose inhaled corticosteroids and an additional controller medication, with or without oral corticosteroids. Patients were required to have had two or more exacerbations in the year prior to enrollment. The primary endpoint of both trials was the annualized asthma exacerbation rate.[20-22]

And in both trials, treatment with tezepelumab showed a significant reduction in the annualized exacerbation rate compared to placebo. In PATHWAY, the reduction was 71 percent, and in NAVIGATOR, it was 56 percent. Both of these reductions in exacerbations were statistically significant compared to placebo.[20-22] Tezepelumab also showed reductions from baseline in type-2 inflammatory biomarker levels, including blood eosinophil count, FeNO, IgE, IL-5, and IL-13. These reductions were maintained over the 52 weeks of the studies.[20-22]

ANNOUNCER:
Let's not forget these results are descriptive only.

Professor Bourdin:
Additionally, a post-hoc analysis of pooled PATHWAY and NAVIGATOR subgroups showed reductions in asthma exacerbations in the tezepelumab group across asthma phenotypes compared to placebo.[23]

Dr Turck:
And before we move on, what were the safety results from these studies?

Professor Bourdin:
The safety profile of tezepelumab was based on the pooled safety population from PATHWAY and NAVIGATOR. This consisted of 665 adult and pediatric patients 12 years of age and older with severe asthma who received at least one dose of tezepelumab.[20]

Adverse reactions with tezepelumab that occurred at an incidence of three percent or greater, and more commonly than in the placebo group, include pharyngitis, arthralgia, and back pain—each at 4 percent for tezepelumab and 3 percent for placebo.[20]

Dr Turck:
Well, now that we've reviewed the PATHWAY and NAVIGATOR pivotal trials for tezepelumab, let's focus on CASCADE. How was this trial designed? And what were the outcomes of this study?

Professor Bourdin:
Well first, I want to mention that the clinical significance of this data and its impact on asthma haven't been definitively established. CASCADE was an exploratory, Phase 2, double-blind, randomized, placebo-controlled study conducted across multiple centers.[21,22] 116 adults with uncontrolled, moderate-to-severe asthma were randomly assigned to receive either tezepelumab 210 milligrams or a placebo, which was administered subcutaneously every four weeks for up to 52 weeks. Patients had bronchoscopies with biopsy at baseline and at the end of therapy and were followed for 12 weeks after the end of treatment. The primary endpoint was the change in airway submucosal inflammatory cells in these biopsies from baseline to end of treatment.[24]

In this study, patients treated with tezepelumab had an 89 percent reduction in airway submucosal eosinophils compared to 25 percent for those on placebo. In addition, tezepelumab reductions in type-2 inflammatory biomarkers compared to placebo, including blood eosinophils, IL-5, FeNO, and IL-13 were observed.[24]

And finally, a post-hoc exploratory analysis of the CASCADE trial was also performed to look at the potential effects of tezepelumab on mucus plugging in moderate-to-severe asthma.[25]

Dr Turck:
And what did the CASCADE exploratory mucus plug analysis show?

Professor Bourdin:
With the CASCADE trial data, the post-hoc exploratory analysis looked at the connection between anti-TSLP treatment and mucus plugs by assessing mucus plugging on CT before and after tezepelumab treatment.[25] 116 patients were randomly assigned and received study treatment. Out of those patients, 91 had standardized CT scans at baseline and 82 had CT scans at both baseline and end of treatment. An expert radiologist who was blinded to treatment groups performed the patients' mucus plug scoring. The number of lung segments, out of 18 total, with at least one mucus plug determined the total mucus score.[25]

So let's begin with the baseline mucus score distribution, which was similar to what has been reported in previously published studies. And I'll note here that a slight imbalance between treatment arms was observed, with more placebo patients having a score of zero than the tezepelumab arm.[11,25]

At baseline, mucus scores had a positive correlation to inflammatory markers like blood eosinophils, eosinophil-derived neurotoxin, FeNO, IL-5 and IL-13. On the other hand, mucus scores were negatively associated with lung function, specifically FEV1 and FEF25-

75%.[25] Next, reductions in mucus plug scores from baseline to end of treatment in patients taking tezepelumab versus placebo were observed. The population with mucus plugs at baseline showed a 62 percent reduction by the end of treatment.[25,26]

Finally, when examining the changes in lung function parameters compared to the changes in mucus score, the reduction in mucus scores observed with tezepelumab correlated with improvements in lung function parameters.[25] But, I'll note here again that the clinical significance of these outcomes and their impact on asthma haven't been established and these results are descriptive only. And, the mechanism of action of tezepelumab in asthma hasn't been definitively established.[20]

Dr Turck:
Thank you for breaking down key information for us, Professor Bourdin.

Before we close out, I'd like to review the Important Safety Information for TEZSPIRE.

ANNOUNCER:
IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
Known hypersensitivity to tezepelumab-ekko or excipients.

WARNINGS AND PRECAUTIONS
Hypersensitivity Reactions
Hypersensitivity reactions were observed in the clinical trials (eg, rash and allergic conjunctivitis) following the administration of TEZSPIRE. Postmarketing cases of anaphylaxis have been reported. These reactions can occur within hours of administration, but in some instances have a delayed onset (ie, days). In the event of a hypersensitivity reaction, consider the benefits and risks for the individual patient to determine whether to continue or discontinue treatment with TEZSPIRE.

Acute Asthma Symptoms or Deteriorating Disease
TEZSPIRE should not be used to treat acute asthma symptoms, acute exacerbations, acute bronchospasm, or status asthmaticus.

Abrupt Reduction of Corticosteroid Dosage
Do not discontinue systemic or inhaled corticosteroids abruptly upon initiation of therapy with TEZSPIRE. Reductions in corticosteroid dose, if appropriate, should be gradual and performed under the direct supervision of a physician. Reduction in corticosteroid dose may be associated with systemic withdrawal symptoms and/or unmask conditions previously suppressed by systemic corticosteroid therapy.

Parasitic (Helminth) Infection
It is unknown if TEZSPIRE will influence a patient's response against helminth infections. Treat patients with pre-existing helminth infections before initiating therapy with TEZSPIRE. If patients become infected while receiving TEZSPIRE and do not respond to anti-helminth treatment, discontinue TEZSPIRE until infection resolves.

Live Attenuated Vaccines
The concomitant use of TEZSPIRE and live attenuated vaccines has not been evaluated. The use of live attenuated vaccines should be avoided in patients receiving TEZSPIRE.

ADVERSE REACTIONS
The most common adverse reactions (incidence ≥3%) are pharyngitis, arthralgia, and back pain.

USE IN SPECIFIC POPULATIONS
There are no available data on TEZSPIRE use in pregnant women to evaluate for any drug-associated risk of major birth defects, miscarriage, or other adverse maternal or fetal outcomes. Placental transfer of monoclonal antibodies such as tezepelumab-ekko is greater during the third trimester of pregnancy; therefore, potential effects on a fetus are likely to be greater during the third trimester of pregnancy.

Please see full Prescribing Information, including Patient Information and Instructions for Use at the landing page link below this program, or at TezspireHCP.com

Dr Turck:
And as that brings us to the end of our program, I want to thank my guest, Professor Arnaud Bourdin, for helping us better understand the role of TSLP including mucus plug pathology and for reviewing the clinical efficacy and safety data of tezepelumab. Professor Bourdin, it was great speaking with you today.

Professor Bourdin:

Thank you for having me.

Announcer:
This program was sponsored by Amgen and AstraZeneca. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be part of the knowledge.

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