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Inflammatory Pathways in Severe Asthma: Focus on Mucus Plugs

Announcer:
Welcome to ReachMD. This Medical Industry Feature, titled “Inflammatory Pathways in Severe Asthma: Focus on Mucus Plugs,” is brought to you 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 and underlying clinical outcome pathology of mucus plugging in severe asthma. Professor Bourdin is Head of Pulmonology at Arnaud de Villeneuve Hospital in Montpellier, France. Professor Bourdin, welcome to the program.

Professor Bourdin:
Great to be here.

Dr Turck:
To start us off, Professor Bourdin, can you help us understand why severe asthma is so challenging to treat?

Professor Bourdin:
Absolutely, as when it comes to severe asthma, it's important to keep in mind the recent understanding that it’s actually a complex and diverse disease.[1] We’re now understanding that the pathophysiology of severe asthma is unpredictable and heterogeneous, with various triggers activating several pathways.[2,3] And so, many patients may have multiple drivers of inflammation,[4,5] and as a result, they may express overlapping or changing phenotype.[6]

Given this complexity, it's not surprising that treating severe asthma can be quite challenging.[7] In fact, approximately 60 percent of U.S. patients on treatment for severe asthma, even with new therapies, remain uncontrolled or partially controlled.[8] And as we know, uncontrolled asthma can lead to recurrent exacerbations, which can impact patients.[9,10] That's why it's so important to have options available to help patients reduce their risk of attack, breathe better, and improve symptom control.

Dr Turck:
Now with that background in mind, I’d like to turn our attention to mucus plugs – what’s their role in severe asthma?

Professor Bourdin:
So, mucus plugs develop from type-2 inflammatory airway disease when interleukin-13, or IL-13, promotes mucin production and IL-5 leads to eosinophil-mediated oxidation of the mucin. The mucus that’s produced as a result is different in volume, in composition, and other properties from our typical mucus.[11] This was shown in study comparing the mucus viscosity from patients with asthma, COPD, and non-CF bronchiectasis, where the mucus from asthma was more viscous than the other two conditions.[12] This "pathologic mucus" isn't easily cleared and can lead to plugging of the airway.[11] And these mucus plugs have been recovered from bronchoalveolar lavage of patients with acute asthma exacerbations as well as in autopsies from fatal asthma. In the latter cases, the lungs remain inflated because of air trapping due to intraluminal mucus plugging.[11]

For a visual example, Professor Edward Klatt published a startling photo of an extreme case of mucus plugging forming a bronchial tree cast that a patient coughed up during an acute asthma attack.[13,14] Now, what we’ve only recently learned is that mucus plugging may

be present and persistent in chronic severe asthma as well.[11] In fact, studies have shown that mucus plugs may drive some lung function deficits in severe asthma.[11]

Dr Turck:
I'd like to hear more about that. Professor Bourdin, what's the clinical relevance of mucus plugs in severe asthma?

Professor Bourdin:
Well recently, a study by Tang et al looked at changes in airway mucus plug score from baseline to year three. The researchers demonstrated that change in mucus plug score negatively and significantly correlated with changes in FEV_1 percent predicted, and positively correlated with change in percentage of voxels below —856 Hounsfield units, a measure of air trapping. Also, their results showed that change in blood eosinophils positively correlated with changes in the mucus plug score.[15] Additionally, we've seen that the majority of severe asthma patients have mucus plugs – 68 percent in one study by the NIH-funded Severe Asthma Research Program, also known as SARP, compared to 40 percent of non-severe asthma patients.[16]

Moreover, we've learned that mucus plugs can remain chronic and persistent in patients with severe asthma. In the SARP study, 82 percent of patients who had mucus plugs at baseline had persistent mucus plugs at year three, despite standard treatment.[15] And again, in the Tang study, we can see the clinical relevance of persistent mucus plugging, as these patients were more likely to have a severe airflow limitation, with an FEV_1 less than 60 percent of predicted, than patients who didn't have mucus plugs.[15] Patients with these persistent mucus plugs were also found to experience 2.5 times more exacerbations, be older, more likely to be on chronic oral corticosteroids, have greater airflow limitation, and have features of type 2 inflammation, such as higher eosinophils in blood and sputum, higher fraction of exhaled nitric oxide – also known as FeNO, and history of nasal polyps.

Dr Turck:
And now that we've seen the clinical significance of mucus plugs, how might they be detected in a patient with chronically severe asthma?

Professor Bourdin:
While it may be impractical to test for mucus plugs in the clinic, in a research setting, mucus plugs can be identified on lung multidetector computed tomography, or MDCT for short, which is an imaging technique that can be helpful to assess airway anatomy, airway remodeling, and mucus plug visualization. On MDCT, a mucus plug would show a complete occlusion of the airway.[11] Additionally, SARP has developed a mucus plug scoring system based on mucus plugs visualized on imaging. Each of the 20 bronchopulmonary segments that have at least one mucus plug is counted to generate the mucus score from 0 to 20. Mucus plug scores can be further grouped into low, ranging from 0.5 to 3.5, and high, which is a score of four or above.[11]

Dr Turck:
For those just tuning in, you're listening to ReachMD. I'm Dr Charles Turck, and today I'm speaking with Professor Arnaud Bourdin about mucus plugging in severe asthma.

Now, Professor Bourdin, can you take us through underlying pathways that lead to mucus plug development?

Professor Bourdin:
Sure, so when looking at patients with high mucus scores, researchers found that sputum gene expression of IL-5 and IL-13 were higher than in the patients with a zero or low mucus score. And these differences persisted after systemic corticosteroid treatment.[16] Similar trends were also seen with sputum eosinophils and fraction of exhaled nitric oxide. So, these findings point towards the type-2 inflammatory pathway underpinning mucus plug pathology.[16] And now we have a model, supported by data, that explains how interactions between mucin and eosinophils can lead to mucus plug formation through the type-2 inflammatory pathway.[11] In it, IL-13 stimulates the airway epithelium to secrete high concentrations of mucin into the airway lumen.[11] And IL-5 triggers eosinophils to cause oxidation of this mucin—resulting in the pathologically stiffened mucus which can form plugs that cause airway obstruction.[11]

Dr Turck:
Now that we've reviewed the clinical significance and pathogenesis of mucus plugs, Professor Bourdin, let's turn back to severe asthma. What do we know about how mucus plug formation fits into the inflammatory pathways associated with asthma?

Professor Bourdin:
Let's start with where we left off, the type-2 inflammatory pathway leading to IL-5 and IL-13 release, resulting in eosinophil and mucin interactions that promote mucus plug formation. Now, let's take a step back and start at the top of the inflammatory cascade. This is

where the airway epithelium is crucial in asthma inflammation, as it acts as a physical barrier and environmental sensor.[17,18] The epithelial cells can induce airway inflammation and structural changes when triggered by environmental exposures such as pathogens, allergens, pollutants by rapidly releasing epithelial cytokines, also known as alarmins.[2,17] And upon epithelial damage or immune cell activation, these alarmins can then activate downstream innate and adaptive immune responses.[2,18,19]

Now, in allergy-related type-2 inflammation, type-2 T helper cells, also called Th2 cells, activate eosinophils via IL-5. Th2 cells, together with activated basophils, also trigger IL-4 and IL-13 production, which causes immunoglobulin E, or IgE, class-switching in B cells. IL-5 also acts with IL-13 to activate mast cells. At the same time, cells of another kind called type 2 innate lymphoid cells, or ILC2s, induce production of IL-5 and IL-13 as well—resulting in both eosinophil activation and non-allergic airway inflammation.[1,2,20,21]

So with all that in mind, let's take a look at one of the alarmins that drives these Th2 responses downstream, called TSLP, which stands for thymic stromal lymphopoietin. TSLP triggers these Th2 responses indirectly through dendritic cells and T cells—and it's been shown to play a key role in allergy and asthma pathophysiology.[18] That's because TSLP not only affects type-2 inflammation, but also type-2 independent pathways across allergic, eosinophilic, and smooth muscle-mediated components of asthma.[2,18]

Actually, in taking a closer look into the eosinophilic pathway, we find that TSLP is involved upstream from the release of IL-13 and IL-5—which we'll recognize as the cytokines involved in the development of mucus plugs from our model.[2,11] And so, TSLP is positioned at the top of the inflammatory cascade and can drive multiple inflammatory pathways that contribute to asthma-related airway inflammation, as well as mucus plugging.[2,11,18]

Dr Turck:
Now as we come to the end of our program, Professor Bourdin, what key takeaways would you like to leave with our audience?

Professor Bourdin:
I'd like to emphasize that severe asthma is a complex and heterogeneous disease characterized by airway inflammation and hyperresponsiveness, and as we've recently learned, persistent mucus plugging.[2,11,15] And research points toward mucus plugging resulting from type-2 inflammation.[16] So, understanding the pathways underlying severe asthma is important to improve our care approach for patients with severe disease who remain uncontrolled despite adherence to standard of care therapies.

Dr Turck:
That's a great way to round out our discussion on this subject. And I want to thank my guest, Professor Arnaud Bourdin for helping us better understand the pathogenesis and clinical impact of mucus plugs in severe asthma. Professor Bourdin, it was great speaking with you today.

Professor Bourdin:
Thank you for having me.

Announcer:
This program was brought to you by Amgen and AstraZeneca. If you missed any part of this discussion, visit Medical Industry Features on ReachMD.com, where you can Be Part of the Knowledge.

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