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Investigating T2 Inflammation in Severe Asthma & COPD

Announcer:
You're listening to ReachMD, and this is *Deep Breaths: Updates from CHEST*. This is a nonpromotional, non-CME disease state educational podcast brought to you by the American College of CHEST Physicians in collaboration with and paid for by GSK. Here's your host, Dr. Peter Howarth. Dr. Howarth is a Professor of Allergy and Respiratory Medicine, and Honorary Consultant Physician within Medicine at the University of Southampton. He is also the Global Clinical Scientific Lead at GSK.

Dr. Howarth:
This is ReachMD and I'm Dr. Peter Howarth. Joining me to discuss Type 2 inflammation in patients with severe asthma and COPD are Dr. Geoffrey Chupp and Dr. Ian Pavord. Dr. Chupp is a Professor of Pulmonary Medicine and Director of the Yale Center for Asthma and Airways Disease at Yale School of Medicine. Dr. Chupp, welcome to the program.

Dr. Chupp: Great to be here, Peter.

Dr. Howarth: Great. Thanks. And Dr. Pavord is Professor of Respiratory Medicine at the University of Oxford and an Honorary Consultant Physician at the Oxford University Hospitals. Dr. Pavord, welcome to the program.

Dr. Pavord:
Thank you very much, Peter. Delighted to be here.

Dr. Howarth:
Well, I couldn't think of two better people to draw in the discussion with me about Type 2 inflammation and perhaps we'll dive straight in. Starting with you Dr. Chupp, can you help us define what Type 2 inflammation is and how it relates to allergies and asthma?

Dr. Chupp:
Sure, Peter. Type 2 inflammation is the predominant inflammatory response that's seen in asthma. It is characterized both histologically and at the molecular level. Histologically what you see in the airway wall is the presence of eosinophils and T cells and an increase in inflammation associated with the disease. And at the molecular level, you have increased expression of cytokines including IL-4, 5, and 13, which are the canonical T2 cytokines. But we also now recognize that other cytokines are expressed in this inflammatory response alarmins, including TSLP and IL-33. We also recognize now that there are two subtypes of Type 2 inflammation that probably coexist in many, many patients but sometimes can be relatively independent, such that you see one of the forms of inflammation in some patients and the other form in others, and that is that there's the classic, adaptive immune response, where there is the presence of IgE against an allergen that you can detect in the patient through allergy testing. And then the other type where you see this innate immune response with the presence of innate lymphoid cells that produce a lot of IL-5 and IL-13 and so you see the presence of eosinophils in the airway wall, but you don't have the presence of allergies.

Dr. Howarth:
Dr. Pavord, perhaps I could ask you how does this inflammation manifest itself in patients with asthma and COPD, and is it consistent or is there heterogeneity in these diseases?

Dr. Pavord:
Well, the diseases are heterogeneous and COPD in particular there are many other patterns of airway inflammation and neutrophilic inflammation is probably predominant. The main way that Type 2 inflammation manifests itself is to cause non- bronchodilator response of airflow limitation and it does this through a number of mechanisms. So airway mucus plugging is probably an important mechanism, particularly in the pathogenesis of exacerbations of asthma and COPD. And this formation of hard, sticky mucus plugs that are difficult to

clear and are particularly likely to obstruct airflow that characterize s Type 2 inflammation.

We also see thickening of the airway wall basement membrane thickening and edema, which will impact on airflow. And we have increased numbers of mast cells, typically often intermittently associated with airway smooth muscle where their interaction may induce airway hyperresponsiveness, which also contributes to airflow limitation. But the strongest clinical association with Type 2 airway inflammation is the occurrence of exacerbations of asthma and COPD. These are episodes from the disease that don't respond well to rescue bronchodilators and therefore need emergency treatment.

Dr. Howarth:
Thank you, Ian. There is a lot of focus on Type 2 inflammation and underlying disease at the moment. But for clinicians with patients in front of them, are there any laboratory tests that they can use that help them define whether the patient has Type 2 inflammation or not?

Dr. Pavord:
Yeah, there are two really helpful tests. The peripheral blood eosinophil count and exhaled nitric oxide. They probably reflect different aspects of Type 2 inflammation with exhaled nitric oxide, particularly reflecting the airway mucosal side and IL-13 activity in the airway. And the blood eosinophil count more reflecting the systemic reservoir of circulating eosinophils that could be recruited towards the airway epithelium. And very closely associated with IL-5, so they're complimentary, these two biomarkers.

There is one further biomarker that we should discuss and that's IgE, which is a biomarker of Type 2 inflammation but it's less closely associated with key outcomes than the first two biomarkers of exhaled nitric oxide and blood eosinophil count. And that might, particularly in severe asthma, that might reflect the importance of the innate pathway that Dr. Chupp just talked about in severe asthma.

Dr. Howarth:
Thank you. For those of you just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Peter Howarth and I'm speaking with Dr. Geoffrey Chupp and Dr. Ian Pavord about identifying Type 2 inflammation in patients with severe asthma and COPD.

Perhaps I could just ask a little bit more about the laboratory tests because clearly if the guidelines for management, particularly severe asthma management, encourage their use, we need to understand what their ranges are and how variable they are. Dr. Chupp, can you give some insight into those aspects of the laboratory tests?

Dr. Chupp:
Sure, Peter. I think one of the important things to start with here is to recognize that these are guidelines for cut-offs, and we think of these things because of their variability that we don't have hard stops on what the thresholds are. But generally speaking, and based on the data looking at patients that's been generated in a number of studies, we know that when the blood eosinophil count is 150 cells per microliter or higher in this clinical context of a severe asthma patient who is not well-controlled that this is a marker of the Type 2 inflammation and this is a patient that we now suspect or we might call a severe eosinophilic asthmatic.

And then as Ian mentioned, in those patients who have specific IgE levels associated with their asthma where we know that allergies are contributing to their disease and their environment has something in it that we know is driving their disease that this is asthma that's allergy-driven. So, in the clinical context of severe, uncontrolled disease when you have any of these markers we would call that a refractory or uncontrolled Type 2 inflammation. And recognizing that this needs to be done over time often over months or potentially a year to really nail down if your patient is Type 2 or not because there's so much variability in the values and they can be affected by medications such as inhaled steroids and systemic steroids.

Dr. Howarth:
Yeah, I think you highlighted a very important point there, things are variable and as you highlight that one may need to make multiple measures to fully understand the underlying nature of a patient's disease.

Clearly, you know guidelines are recommending the measurements of these and characterizing the patients and it has to have some implications. How can blocking mediators of Type 2 inflammation impact on outcomes in patients with asthma?

Dr. Chupp:
Well, I think we've all been fortunate to be part of this revolution in terms of both improvement in our understanding of the pathogenesis of disease and the recognition of the importance of Type 2 inflammation but with this over the last 30 years has come the development of targeted therapies against these key molecular mediators of the disease . Most of these monoclonal antibodies have been targeted against T2 cytokines and IgE. So, modulating these has really proven to reduce the T2 inflammation in these patients and that leads to much improved control of their disease; reduction in exacerbations.

Dr. Howarth:

Geoff, thank you very much. It really has made a substantial difference to patients recognizing the underlying Type 2 inflammation and targeting that in terms of improving disease outcomes.

So, before we close, perhaps Dr. Pavord I can ask you if you could perhaps review some of the lessons we've learned. And how do you think that an improved understanding will impact on how we deal with airways disease in the future?

Dr. Pavord:
I've been doing severe asthma for a long time and it really was in the old days a matter of managing an orderly decline and the patient accumulated more and more problems and some of them related to the treatment we needed to give them, particularly oral corticosteroids and it was a tough problem to deal with. But, now we have these biologic drugs which very selectively inhibit this process, Type 2 airway inflammation. And when given to the right patients have a very big clinical impact and we've got predictive biomarkers that are easy to measure and are highly predictable of the efficacy of treatment and more importantly, the outcome. So, we have treatments that targeted what I like to call a treatable trait, which is a measurable aspect of the disease that's driving important clinical problems. And that's been a huge boost and there are other treatable traits in airways disease that we need to define carefully, we need to make measurable, and we need to be able to inhibit that selectively with drugs. And I think that's the way forward.

With the drugs that target Type 2 inflammation, I mean, their clinical impact in severe asthma has been large. Clearly we're beginning to think about should these drugs be used earlier. And so currently we wait for patients to get quite badly damaged by the Type 2 inflammation before we treat. And often we can turn things around but not always; sometimes there's irreparable damage. And maybe the future and of course, this does require a lot of work and studies, is to identify patients who by dint of their biomarker profile are going to do badly so they have very high biomarkers of Type 2 airway inflammation which can't be controlled with inhaled steroids and say, right, well we probably need to get in and treat this process now before you become irreparably damaged by it.

Dr. Howarth:
Thank you very much for those forward-looking thoughts. I think clearly the availability of biologics is opening up new horizons for our patients with asthma and potentially in the future for COPD.

So, I want to thank my guests today, Dr. Geoffrey Chupp and Dr. Ian Pavord for joining me to talk about Type 2 inflammation in patients with severe asthma and COPD. Dr. Chupp, Dr. Pavord, it was a great pleasure speaking with you today. Thank you.

Dr. Chupp:
Great discussion Peter, thank you so much.

Dr. Pavord:
Yeah, thank you Peter, it was great to talk to you both. Many thanks.

Dr. Howarth:
I'm Peter Howarth and I thank you all for listening in to this exciting podcast. Thank you.

Announcer:
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