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Treatment Options in Non-Type 2 Asthma

Announcer:
Welcome to CME on ReachMD. This activity, titled “Treatment Options in Non-Type 2 Asthma,” is brought to you by CHEST. This educational activity is supported by an educational grant from GlaxoSmithKline and an educational grant from Genentech, a member of the Roche Group.

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Here’s your host Dr. Sandhya Khurana, Professor of Medicine at the University of Rochester and Director of the Mary Parkes Center for Asthma, Allergy, and Pulmonary Care.

Dr. Khurana:
Among the approximately 300 million people who are affected by asthma worldwide, various phenotypes exist that require an individualized approach to treatment. Today we’ll be exploring one of the particularly challenging phenotype of non-type 2 asthma and learn more about how we can tailor our management approach for these patients.

This is CME on ReachMD, and I’m Dr. Sandhya Khurana. Joining me to discuss treatment options for non-type 2 asthma is Dr. Fernando Holguin, Professor of Medicine-Pulmonary Sciences & Critical Care as well as Director of the Asthma Clinical and Research Programs at the University of Colorado School of Medicine.

Dr. Holguin, welcome to the program.

Dr. Holguin:
Thank you, Dr. Khurana. I appreciate the invitation. I’m delighted to be here.

Dr. Khurana:
So, Fernando, to start off, can you give us a brief overview of what non-type 2 asthma is?

Dr. Holguin:
Sure. The way I think about non-T2 asthma is that it’s a very common phenotype. Roughly about half the patients that you will see in the clinic are not going to have some of the typical biomarkers that we normally think are associated with type 2 asthma, which are higher levels of exhaled nitric oxide, elevated peripheral blood eosinophils or sputum eosinophils, and perhaps to a less extent higher IgE levels. So these patients are common. They often don’t respond to inhaled corticosteroids as patients with more predominant type 2 asthma do, and so they are challenging to manage from a clinical perspective.

Dr. Khurana:
I think we all know when we see type 2 asthma we are able to recognize it, but sometimes I feel non-type 2 asthma really is a diagnosis of exclusion where you’ve ruled out some of the type 2 characteristics. So, how do you define or how do you try to identify non-type 2 asthma in your practice?

Dr. Holguin:
That's a very good question. It's a challenging part because, in fact, we are defining a phenotype by something that they don't have and the biomarkers may not tell the whole story; there may even be some degree of type 2 inflammation, but we were not able to detect it with the biomarkers that we have on hand clinically. So I normally think about these patients as those that, when you see them, they don't have any of the typical biomarkers that I just mentioned briefly that are elevated. But one needs to be careful that you're not confounding issues that relate to prior medication use because many of these patients, for example, have been on systemic corticosteroids and some other medications that could perhaps influence how you perceive them to be. So, once I'm sure that those patients don't have any evidence of type 2 biomarkers, I tend to think about them as having a non-predominant type 2 asthma and potentially think about different types of treatment alternatives for them.

Dr. Khurana:
Dr. Holguin, thank you so much for giving us some background to the non-type 2 asthma. And I know that we understand the mechanisms in play in type 2-high asthma quite well, but what is the current understanding of the pathobiology of mechanisms underlying non-type 2 asthma?

Dr. Holguin:
Yes, that's a really interesting question. We have to first understand that subjects or patients with non-type 2 asthma really comprise of a very heterogeneous group of patients that may have very different mechanisms or pathways that eventually lead to airway injury, inflammation, or airway dysfunction, and those can really come from longstanding exposure to pollutants, to viruses, to inhalation of other products or to exposure of endogenous metabolic disturbances that eventually lead to some of these pathways to become more activated.

Some of these patients may have, from epithelial gene expression studies, greater activity of Th1-related inflammation, such as different types of interferon-gamma responses. Th17 responses have also been involved as well as IL-6 levels, particularly in some obese asthmatics. But again, this is a highly oversimplification of a much more complex immune response in these patients.

Dr. Khurana:
So, it sounds like there are multiple endotypes and subphenotypes within this broad bucket that we're calling non-type 2 asthma. Would you agree, Fernando? And what are the different subphenotypes that you usually think about when you're considering this type of asthma?

Dr. Holguin:
That's a good question, Sandhya. So we normally think about type 2 asthma as those with more allergic early-onset disease, and perhaps those a with later onset have predominant severe eosinophilic asthma, but non-type 2 asthma, as you mentioned, is this sort of black box that encompasses many different phenotypes. So there we have, for example, related to obesity, particularly late onset in females. There are patients there that have potential for neutrophilic-predominant airway inflammation that lack type 2 biomarkers, and there are also patients in whom their disease appears to predominantly affect airway smooth muscle, and they have very little inflammation, and so, many of these patients can present later on with fixed airway obstruction.

Although there are many different phenotypes compared to type 2 asthma, some of these patients may have perhaps less impaired lung function. They certainly have perhaps a lower degree of bronchodilator responsiveness, but they are less responsive to inhaled corticosteroids.

Dr. Khurana:
For those just joining us, this is CME on ReachMD. I'm Dr. Sandhya Khurana, and today I'm speaking with Dr. Fernando Holguin about non-type 2 asthma.

So, Dr. Holguin, let's dive a little bit deeper and talk more management. I know there are a lot of challenges in management of non-type 2 asthma, and we are still ways away from targeted therapy. And you mentioned there are no specific biomarkers that have been identified, but are there any that are under study or in research that we might expect to see in the future?

Dr. Holguin:
Well, as you mentioned, Sandhya, there's really no adequate treatment for these patients when you're dealing with the patient with non-type 2 asthma, and one of the things you commonly see is that these patients have been treated with lots of steroids and still are very symptomatic, so we definitely must look for other potential avenues of treatment, particularly given the potential risk that steroids may at some level make things worse for some of these patients.

There are different treatments that either could be specific or that function equally well in patients with type 2 and non-type 2 asthma. For example, some of the inhaled medications like anticholinergic drugs or muscarinic antagonists like tiotropium, for example, those

drugs can be adequate bronchodilators that can work on both types of type 2 and non-type 2.

There was a recent study published in the New England Journal of Medicine by AsthmaNet called the SIENA Study that evaluated response of tiotropium based on sputum eosinophil levels and found that in naive patients to inhaled corticosteroids with mild persistent asthma, those that had no eosinophils ended up responding better to tiotropium as an entry drug. So I think we need to look at our patients and try to identify that lack of non-T2 biomarkers to identify better treatments for them. So tiotropium is one.

Another one that could potentially work for patients to reduce frequency of exacerbations is macrolides, like azithromycin. Earlier studies have shown that patients with non-eosinophilic disease would preferentially respond better, but subsequent studies and large randomized controlled studies have shown that both eosinophilic or non-eosinophilic disease eosinophilic asthma phenotypes can respond to macrolides, and we have as much as 20-25% reduction in exacerbations. So those are some of the drugs that are available to clinicians that they could potentially use in some of these patients.

There's a new drug that's likely moving through phase III that's called the anti-TSLP tezepelumab, which is a monoclonal antibody that targets cytokine-derived lymphopoietin, which sits high at the chain of inflammatory response, and the phase II studies show that this monoclonal antibody can potentially reduce the frequency or exacerbations and improve health in people regardless of whether they have type 2 biomarkers or not.
So those are some of the treatments that I think are going to become available, and there is certainly a host of other potential metabolic drugs that act through different pathways that could affect airway function as well.

Dr. Khurana:
Great, thank you. From what I'm hearing, if somebody has neutrophilic asthma or frequent exacerbations, then macrolide could be an option. If somebody has airflow limitation and non-eosinophilic asthma, a long-acting muscarinic or anticholinergic would be an option.
Do you feel there's a role for thermoplasty, or do you ever consider that in your patients?

Dr. Holguin:
Thermoplasty, personally, I think we're still learning a lot how this innovation works. The current guidelines suggest that this approach be limited to centers that have expertise and registry, but certainly I think it's an option to patients that lack any type of type 2 biomarkers and have been unresponsive to therapy. But like anything else, Sandhya, I think you have to try to match as best as possible which is the right patient for the right treatment. So I think there's a subset of people from whom bronchial thermoplasty can be useful. We may not know exactly the correct sort of definition as to who is that patient population, but there are certainly groups that could benefit from it.

Dr. Khurana:
Thank you, Fernando, for that information. And last but not least, I know that metabolic dysfunction and obesity in asthma is an area of special interest to you, and I was wondering what your thoughts were, if you could share some pearls and how we could manage obesity-associated asthma.

Dr. Holguin:
Thanks, Sandhya. I'm glad you asked that question since it really relates to work that we've been doing here for some time. It's important to remember that in patients with asthma and obesity, it's not only about the weight. There are factors such as metabolic syndrome and even diabetes or poor glycemic control that have been, independently of BMI, implicated in airway dysfunction. Our group has been very interested in understanding how obesity and metabolic disruptions impair the production of endogenous bronchodilators that are derived from nitric oxide in the airways, and we've shown that in patients with obesity, particularly those with late-onset disease, they have less nitric oxide, and they might produce less of some of these important bronchodilators that maintain normal airway function.

It's interesting that patients with obesity and asthma also have very significant abnormalities in mitochondria function and regulation in the airway epithelium, and we don't know yet what the clinical implications of having abnormal mitochondria, but we do know, in fact, that the metabolism of the airway in these patients is very different than those that are lean. All these factors could either make the patient more symptomatic by being related to abnormal airway function or potentially could impair the response to drugs such as inhaled corticosteroids and other controllers. In that regard, I think, while there's no specific treatment for obesity-related asthma, weight loss has been shown to have potential for improving outcomes, and so that should always be recommended to patients.

There are a number of potential interventions to improve the health of subjects with obesity and asthma that have not yet made it into the clinical realm of things, or they haven't been tested sufficiently enough. One of them is L-citrulline, which my group has been working on with the idea to increase nitric oxide in the airways and increase the production of some of these endogenous bronchodilators. There are other drugs that are currently being investigated through PrecISE NIH Network like anti-IL-6. Some patients with increased BMI have higher levels of these cytokines and potentially could benefit to a greater extent than patients who are leaner. So I think these are

some examples of treatments that are being explored.

There are other trials that are being investigated—with MitoQ, for example—to try to improve mitochondrial function. I think in the next several years we will see a number of drugs that might be available specifically to improve the respiratory health of those that experience obesity and asthma.

Dr. Khurana:
And lastly, Dr. Holguin, what are some of the unmet needs? And what research is currently being done that we can look forward to?

Dr. Holguin:
Yes, so I think one of the unmet needs is to recognize that patients with non-T2 asthma are not a unique group of patients. They don't have one disease, but they have a multitude of different diseases, so we need to really work hard in identifying biomarkers that give some idea about the underlying mechanisms of disease or that may potentially give us more information about what is the best drug to treat some of these patients.

There are some simple things that I think could begin to be used more frequently and will make a big difference, is trying to understand, for example, some of the demographic characteristics of the patient; like what is the age of asthma onset in a patient can give a lot of information regarding whether somebody may have a more allergic type 2 underlying disease, or somebody who developed asthma in their late 40s perhaps has a completely different disease phenotype. And so these things certainly in the clinic can help us start to think about what is the initial treatment approach in some of these patients, particularly the ones that are more complicated or have not responded to standard therapy.

Dr. Khurana:
Great. Thank you so much, Fernando. These are really some great insights that you gave us today and we need to consider as we come to the end of today's program.

And I'd like to thank my guest, Dr. Fernando Holguin, for speaking with us about non-type 2 asthma. Dr. Holguin, it was a pleasure to have you on the program. Thanks so much.

Dr. Holguin:
Thank you, Sandhya. The pleasure is all mine.

Announcer:
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