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Precision Medicine in COPD: Eosinophils and Exacerbation History

Announcer:
This is *On the Frontlines of Obstructive Lung Diseases* on ReachMD. Here's your host, Dr. Shelina Ramnarine.

Dr. Ramnarine:
Welcome to *On the Frontlines of Obstructive Lung Diseases* on ReachMD. I'm Dr. Shelina Ramnarine, and today, we'll learn about escalating therapy for patients with chronic obstructive pulmonary disease, or COPD, using eosinophil levels and exacerbation history. Joining me for this conversation is Dr. MeiLan Han, who's a Professor of Medicine and Chief of the Division of Pulmonary and Critical Care at the University of Michigan Health. Dr. Han, we're so glad to have you here.

Dr. Han:
It's great to be here. Thank you, Shelina.

Dr. Ramnarine:
Let's start with the big picture, Dr. Han. How has the "treatable traits" framework changed COPD management relative to the traditional, spirometry-driven, one-size-fits-all approach to therapy escalation?

Dr. Han:
Well, I'll admit, for some reason, I've never been a huge fan of the term "treatable traits," but I do like the concept, which is… essentially, it's precision medicine. We need to do a better job of understanding what's going on at an individual patient level, and try to treat them accordingly, just like you said. We need to stop with the one-size-fits-all approach.

I think one of the biggest changes is that we've stopped assuming that FEV1 or measure of lung function—while important—just simply doesn't tell us everything we need to know about a patient. Yes, it helps. It's essential for a diagnosis. It's also essential for helping to understand disease severity—if a patient's super severe and they need to be moved on towards lung transplant, or something like that. But it's a relatively poor guide when we're trying to figure out which inhaler, or even which biologic, a patient should be on.

And so the treatable traits framework really asks, instead, what is driving risk? What's driving symptoms in this particular patient? And is there something about it that's actionable? So some of those things that might be actionable, particularly right now, are eosinophilic inflammation or type two inflammation, or patients who have recurrent exacerbations, who have chronic bronchitis or emphysema, who are smoking, or who have bronchiectasis or specific comorbidities. We're really looking for things that we know have very specific therapies. And so it moves us away from treating that label of COPD and more towards treating the biology and the clinical phenotype of the individual patient.

Dr. Ramnarine:
Now, blood eosinophil count has become central to that framework. What's the biological rationale for using it as a biomarker in COPD?

Dr. Han:
When I was in med school, COPD really was taught and has been thought of as a predominantly neutrophilic disease. And so the fact that there is a subset of patients that have more eosinophilic or type two inflammation—I was a non-believer for quite some time. But the data is the data, and it's hard to ignore the data.

And it, in fact, shows us that blood eosinophils are associated with more frequent exacerbations, at least in a subset of patients, and, in some patients, actually more rapid lung function decline. The nice thing is that it's pretty readily and easily available. And it does help us to understand which patients are more likely to respond to inhaled corticosteroid therapy. It now also helps us to understand which

patients might be amenable to some of the new selected biologic therapies that also target type two inflammation. So it really is becoming helpful for us as a predictive biomarker in COPD.

Dr. Ramnarine:
We know that guidelines use eosinophil thresholds to inform decisions on adding inhaled corticosteroids. So how do you apply those cutoffs in practice, and how much weight do you give a single measure versus trends over time?

Dr. Han:
Eosinophils actually are a continuum, and they're also highly variable. And despite the fact that the GOLD document puts numbers in there with what feel like magic thresholds, they really aren't. But the data would say, generally speaking, that if levels that are consistently below 100—if you have a patient with levels that are always just rock-solid low—they probably are not going to receive huge benefit from inhaled steroids.

Having said that, I think the number of patients who fit in that category is pretty low. And also, remember that patients move over time. I have had patients who, for a couple-year period, are high, and then they go low. And I don't know—it might be allergens they're exposed to. It's hard to know.

Now, the other threshold that GOLD lists is this 300 threshold, and that is where, above 300, the probability of benefit from some of these biologics like dupilumab or mepolizumab that target type two inflammation becomes greater. I think 100 and 300 are also a bit more of a gray zone. But I think that what you again have to remember is, if I have a patient in that group, and they are having frequent exacerbations, I may check the eosinophil count a few more times, because it really is highly variable. It can be influenced by things in the environment and infections. It can also be influenced by, let's say, a patient got a steroid course for one reason or another.

So I tend to look at that spectrum, and when I do see variability, it really doesn't bother me. What I'm really looking for is at least one high one in the last year or two. Because if I see one high one—and when I say high, I mean roughly 300 or more—to me, it suggests that the patient has evidence of type two inflammation.

Now, if I'm not 100 percent sure, there are other things you can do. You can also check, for instance, a FeNO level, which can be impacted by current smoking, so just know that. But in a patient who's not actively smoking, if that's elevated, that can give me additional information to reassure me that, yes, this patient has evidence of type two inflammation and might respond to a type two inflammation-targeted biologic.

Dr. Ramnarine:
Alongside eosinophils, exacerbation history is often described as one of the strongest predictors of future risk. With that in mind, how can clinicians weigh these two factors together when making escalation decisions?

Dr. Han:
So I think of eosinophils and exacerbations as helping me to answer two different questions. Exacerbation history tells me about how much risk the patient has for a future event. Eosinophilia also tells me a little bit about that, but it also tells me about which therapies might reduce that risk.

So in a patient with recurring exacerbations and elevated eosinophils, I'm thinking not just inhaled steroids, but I'm also thinking about one of these biologics that we've talked about that target type 2 inflammation. So the two pieces of information really become most useful when they're interpreted together.

Dr. Ramnarine:
For those just tuning in, you're listening to *On the Frontlines of Obstructive Lung Diseases* on ReachMD. I'm Dr. Shelina Ramnarine, and I'm speaking with Dr. MeiLan Han about COPD treatment escalation.

Dr. Han, now that we have some background on this approach to escalation, I'd like to talk about some of its limitations. Where can we run into challenges, whether that's variability in eosinophil counts over time, patients who don't fit the typical pattern, or gaps in the evidence?

Dr. Han:
We still have a lot of limitations. There's still much about the disease biology at an individual patient level we don't know. One of the challenges that I mentioned are that eosinophil counts fluctuate. But there are a lot of other things that also cause exacerbations.

We do have some medications that are available that target these patients with elevated eosinophils, but I'm looking forward towards and excited about some of the data coming out about the rest of the patients, and what other therapies we have that might target patients, for instance, who have primarily neutrophilic disease.

I think another challenge is that a lot of the patients that have been included in these clinical trials—in order to get enough signal to get the drugs approved—are patients with super frequent exacerbations. But that maybe tells us a little bit less about patients who have intermittent exacerbations.

And then another thing which we really haven't talked much about today but is related to exacerbations, is just this whole concept of disease progression. We don't know a lot about how the treatments that we have impact longer-term events like lung function decline over the course of years. I mean, we think that they probably help to reduce it, but one of the challenges is that those kinds of clinical trials are also really difficult to conduct—keeping patients in clinical trials for a really long period of time.

So there's still a lot we don't know, but I think the good news is that, because of these initial successes we've seen with biologics in a subset of patients, it's gotten a lot of people excited that there is hope. And so there's so many clinical trials going on right now with lots of other new drugs that are targeting different pathways. And so my hope is that, in the next few years, we'll have more and more to offer patients with COPD.

Dr. Ramnarine:
I'd love it if you could walk us through your actual decision-making process. How do you sequence escalation from LABA/LAMA to triple therapy, and at what point does a patient move from that standard pathway into biologic-eligible territory?

Dr. Han:
So right now, if you look at the GOLD document, the way it's written sometimes is confusing, but I think in reality it's not. You just have to walk through it. So for an initial start, in patients who totally brand new, just diagnosed with COPD, not on anything, the usual initial medication's going to be, as you stated, a LABA/LAMA. So that's a long-acting beta agonist plus a long-acting muscarinic antagonist. If the patient has a strong history of asthma or concomitant asthma or a really high eosinophil level, you might start with triple therapy. But for most patients, it's going to be LABA/LAMA.

And then GOLD suggests that the escalation from there really depends on what you're trying to target. If you're trying to target shortness of breath primarily, that's when you make sure patients are using their medications right. You look for other causes. There is a medication we have not talked about at all today, and that's ensifentrine. And ensifentrine is a nebulized PD3/PD4 inhibitor. It causes significant bronchodilation and can help with dyspnea. It may also help reduce exacerbations—the clinical trial data suggests that, although, because the data isn't really as definitive as it is with some of the other studies we have, it's still, at least in the GOLD document, left on the dyspnea portion of the pathway.

If a patient is having frequent exacerbations and that's what you're trying to target, then the first thing you would do would be to add inhaled steroids if the patient's just on LABA/LAMA. Again, that's for the patients with EOS of 100 or more. And then, if the patient is still having exacerbations beyond that and they're on triple therapy, then you have a couple of options.

If they have EOS of 300 or more, GOLD recommends that's where we consider some of these biologics that target type two inflammation—that would be mepolizumab or dupilumab. For other patients, the two other options at this point include roflumilast, which is best suited for patients with really frequent exacerbations, low levels of lung function, and chronic bronchitis, and then azithromycin, which is best suited for patients who are not actively smoking.

So that's how GOLD breaks it down. But having said that, I am actually anticipating some additional FDA approvals in the next year. And so I suspect that this is probably going to change, and if we were to have this conversation next year, it would look a little bit different. But that's kind of where it stands right now.

Dr. Ramnarine:
Finally, Dr. Han, let's look ahead a moment. Are there other biomarkers, tools, or techniques on the horizon that might refine this approach further?

Dr. Han:
There are other things that we're looking at. Fraction of exhaled nitric oxide can help us identify patients with type two inflammation. That is actively being used. Another biomarker that I think is maybe closer to primetime than some of the others are some of the CT imaging biomarkers. So emphysema already helps us identify patients that may benefit from advanced therapies like lung volume reduction procedures and transplant. There's a lot of active investigation right now in mucus plugging and the use of that as a potential biomarker to help us identify both increased risk as well as patients that might benefit, again, from specific biologic therapies.

And then there's a bunch of stuff going on in more of the investigational space: other blood biomarkers, combinations of biomarkers that, potentially, could be helpful. So I think some of the maybe more sophisticated, more advanced—patient gives their blood, you get some fancy report back that says, "Give this drug, give that drug"—that's a little ways off still. But I think we're definitely getting closer to that.

And I'm really excited about what the next few years are going to bring for COPD research.

Dr. Ramnarine:
That's a great comment for us to think on as we come to the end of our program. A big thanks to my guest, Dr. MeiLan Han, for joining me to discuss how we can optimize COPD care with the help of eosinophil counts and exacerbation history. Dr. Han, thanks so much for being here today.

Dr. Han:
Thanks for having me.

Announcer:
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