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ReachMD
www.reachmd.com
info@reachmd.com
(866) 423-7849

What Type 2 Inflammation in COPD Means for Treatment Decision Making

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This series is produced in partnership with the American College of Chest Physicians, and this episode is a non-promotional, non-CME educational program brought to you by CHEST in collaboration with GSK. And now, here's your host, Dr. Stephanie Christenson.

Dr. Christenson:
Welcome to *Deep Breaths: Updates from CHEST* On ReachMD. I'm Dr. Stephanie Christenson, Associate Professor at the University of California San Francisco in the Division of Pulmonary, Critical Care, Allergy, and Sleep Medicine. I serve as an attending physician at UCSF on the consult service and in the pulmonary clinic.

Joining me to explore the pathobiology of type 2 inflammation in COPD and what it means for treatment decision making is Dr. Diego Maselli. He's a Professor of Medicine at the Long School of Medicine at UT Health in San Antonio.

Diego, thank you for being here.

Dr. Maselli:
Thank you so much, Stephanie. It's a pleasure to be with you today.

Dr. Christenson:
I'm really happy that we get to talk about this. So, just to kick things off, I'm going to just briefly walk us through what type 2 inflammation is—particularly, what type 2 inflammation in COPD is and why it matters.

So, when we think about type 2 inflammation, it's usually something that we would consider more of an allergic type of inflammation. But really, it is driven by TH2 cells and ILC2 cells that make specific cytokines like IL-4, IL-5, and IL-13, which are really important because those are what we direct therapies against. And the production of those cytokines leads to activation of certain cell types like eosinophils and mast cells as well as driving macrophage changes. So, we have a lot of different components of type 2 inflammation that lead to this downstream effect.

In COPD, we find that type 2 inflammation is important, at least in a subset of our patients, and could contribute to the pathophysiology of exacerbations and symptoms. That's super important for COPD because exacerbations really increase morbidity in our patients and can even increase the mortality in our patients. So, it's really important that we try to get them under control and try to prevent them as much as possible. And so now, we have a couple of new drugs in our arsenal that can potentially help us control exacerbations.

So, with all that in mind, I'd like to turn it over to you, Dr. Maselli, and get an idea of how we should interpret the biomarker that we use to identify type 2 inflammation in COPD—blood eosinophil counts. How do you use blood eosinophil counts when identifying patients with type 2 COPD or eosinophilic COPD, depending on how you want to phenotype those patients?

Dr. Maselli:
Thank you so much, Stephanie, for that question. I think it's very important to mention that eosinophils are really easy to measure, so we typically just get a CBC with a differential. Fortunately, it's not an expensive test, so it's readily available for us and for our patients. And it's important to mention that this information can be tracked over time, so you can look back at your medical records and see what happened weeks, months, and even years before. So, it's easy to measure.

Eosinophils can be used to assess the risk of our patients with COPD and also potentially guide our therapies, both in inhaled corticosteroids, and, as you mentioned, now we have two biologics. Very importantly—I think also this is really a key message—high

eosinophils, when we measure them, have been associated with poor outcomes: higher risk of exacerbations, for example, more ER visits, more admissions to the hospital, and even more readmissions to the hospital as well.

So, it's an important way of identifying who might be at risk for poor outcomes down the line.

As I mentioned before, eosinophils can help us guide therapy. For example, higher values have been used to determine if a patient may benefit from inhaled corticosteroids, and there's different cutoffs. A blood eosinophil count of more than 150 cells per microliter may indicate that the patient may have ongoing type 2 inflammation. As you described, these important cytokines that are activated and a level of 300 cells per microliter or above have been linked to a stronger treatment response to biologics, such as mepolizumab and dupilumab.

Dr. Christenson:
And I think that's super important. We know that some of these types of inflammation are really on a continuum, and it is important to realize that we use these beyond just looking for who should be on a biologic. We use these to really help us guide inhaled corticosteroids. Like you were saying, if somebody's actually less than 100, those are patients where I really would avoid using inhaled corticosteroids, and as long as we're testing that during stable periods where they're not on oral corticosteroids, that could suppress our blood eosinophil count.

So, I agree with you. I like to test in really any of my COPD patients who I think might be at risk for getting exacerbations so that I know what my levels are. And I like to test more than once because there can be variability—in fact, even just diurnal variability, but certainly variability when we are at exacerbations, particularly when somebody is getting put on steroids. So, sometimes it's actually helpful to test during the exacerbation and before the steroids because you might see higher levels. Or, if you do see lower levels, maybe that gives us some clue to what's happening as far as, should we be using inhaled corticosteroids or type 2 inflammatory medications? Because we want to use them in the right people, not just everyone. But it does really help us document what our phenotypes are. So, is this an exacerbation prone patient who also has type 2 inflammation where I want to make sure they're on inhaled corticosteroids and might consider a biologic if they're still not controlled on all the appropriate medications and with the appropriate other therapies, like pulmonary rehab and making sure that they're taking the inhalers? So, I check them more than once, maybe multiple times just to make sure that I'm really capturing type 2 inflammation if it's there. What do you do?

Dr. Maselli:
Yes, I follow the same practice. I like to check and recheck and, as you mentioned, I think oral steroids, because they can affect eosinophil counts, we want to make sure that the patient's not on steroids as we check them. Sometimes they even are on chronic steroids on a day-to-day basis because they are very sensitive to steroids, and we don't want to miss those patients that have that eosinophilic phenotype who could potentially benefit from these therapies.

Dr. Christenson:
I completely agree with you.

For those just tuning in, you are listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Stephanie Christenson, and I'm speaking with Dr. Diego Maselli about type 2 inflammation in COPD and how it can inform patient care.

So, Diego, let's talk about treatment escalation. For patients who remain uncontrolled on triple therapy, when should we begin thinking about biologic add-ons, and how do the GOLD 2025 and 2026 guidelines fit into that picture?

Dr. Maselli:
Yes, Stephanie, that's a very important question. When we're thinking about adding biologics, we look for those patients who have frequent exacerbations, particularly those who've had two or more moderate exacerbations or one severe exacerbation over the past 12 months, and those who have elevated blood eosinophils despite good inhaler adherence.

The GOLD 2026 report uses 300 cells per microliter as a guide, but trial evidence supports that lower thresholds for some biologics can be useful, such as mepolizumab. In a therapeutic trial, it's important in a group of selected patients, like the ones I just described, we should treat for at least several months. I think most argue that we should do a therapeutic trial of four to six months. And some patients may have this exacerbation season; for example, patients are triggered by viruses during the winter months. So, I think that the trial should include those months in this group of patients. Of course, every patient is different, so we need to adapt to each patient on a patient-to-patient basis.

Exacerbation reduction continues to be our primary treatment goal for these patients. I think to see that reduction, we need to use the therapy for several months to evaluate that response. We typically have our patients come back to the clinic several months after they start these therapies for an assessment and to evaluate their response.

Dr. Christenson:
I think that's such a good point, and it actually gets at how important the exacerbation is. Even GOLD has recently changed who falls into the GOLD E category or exacerbation phenotype to being either one moderate, meaning they just get oral steroids and are not seen either in the emergency room or the hospital—so one moderate or one severe is now considered a GOLD E patient because we now understand the burden of some of these events, but understanding that original trials were done in patients who had at least two exacerbations that were moderate or one severe.

So, it is an interesting shift there. We're thinking about how important these exacerbation events are, and I would say we really want to try to prevent them because they can cause issues with patients' quality of life and even potentially for mortality. And it's such a good point, Diego, that you made, that these patients are complex. They already have fixed airflow defects, and we're not just going for symptoms. We are really going for that exacerbation control. So, making sure that we have these trials that are looking at trying to reduce exacerbations as the main outcome, which can take several months, is such a great point, Diego. So, thank you for that.

Dr. Maselli:
Of course.

Dr. Christenson:
So, another big piece of this conversation is how we can reduce inappropriate corticosteroid use. And we know that we don't support in our guidelines or in the GOLD report using chronic corticosteroids, although we, of course, need to use them for exacerbations. This is particularly an issue in underserved communities or marginalized communities where they may not have as much support, so we can see this chronic oral corticosteroid use, and that really can be a big issue for a patient who is older and who has a lot of comorbidities already. And chronic OCS use can actually increase both mortality and contribute to comorbidities like osteoporosis, diabetes, cataracts—things that are just monumental for these patients.

So, we really do want to try to avoid doing that when possible. And there is hope that by making sure that we have patients on the appropriate therapies, so eosinophil-guided treatment, whether that means appropriately having them on the appropriate inhalers and biologics, if that's useful, but also making sure that they're taking their medications appropriately, that they're getting their appropriate vaccines so that they can potentially avoid precipitating exacerbations from viruses, that they're getting referrals to rehabilitation, which can greatly improve quality of life for patients and decrease hospitalizations, and really working on those strategies through shared decision making—it's really important that we're really thinking of that full spectrum of care for underserved patients. So, that means patients in inner city communities and patients in rural communities who may lack some access to full spectrum COPD care.

Dr. Maselli, before we wrap up, I wanted to hear from you—what are the key messages you want listeners to take away when it comes to optimizing COPD care for patients with type 2 inflammation?

Dr. Maselli:
I think we're in a different era now in COPD. I think we need to continue to emphasize that there are patients with COPD who are really at higher risk than others. I think we have to continue to ask this question about exacerbations—"How often have you had these events?" and probe a little bit deeper so we don't miss these patients who are at risk. Of course, we need to ask them about their symptoms, but I think focusing on exacerbations is really what the trend is. And then, you mentioned the GOLD report from 2026 emphasizes having a little bit of a lower threshold than before on acting upon exacerbations.

Phenotyping COPD patients, as you mentioned before, it is now more important than ever so that we can tailor their therapies better. I think the blood eosinophil counts are very helpful to risk stratify these patients and potentially select therapies to improve outcomes.

What about you, Stephanie? What are your key takeaways?

Dr. Christenson:
I really liked one of your key takeaways—that we're really trying to reduce burden for patients. And so, some of that is making sure that their symptoms are controlled and their quality of life is better. And some of that is really focusing on the exacerbations because those really can be devastating for many of our patients and trying to get ahead of what's happening as opposed to waiting until they've had multiple exacerbations or until they're feeling really horrible.

I like to work on preventive care as much as possible up front. Sometimes, that does involve increasing inhaler therapy, adding things like biologics, and really working on holistic care; working on making sure that their comorbidities are treated, making sure that they're working on staying active, and using pulmonary rehab as much as possible; and working on smoking cessation and just making sure that this is kind of part of a holistic care approach, but realizing that each patient is really individual. If they have that type 2 inflammation, we should really be working on treating it.

So, for me, that's my takeaway, and I like hearing how we align somewhat on all these issues.

Dr. Maselli:
Absolutely. Yes, definitely. I think we're pretty aligned here.

Dr. Christenson:
So, those takeaways bring us to the end of today's program. I want to thank you, Diego, for joining me to discuss the pathobiology of type 2 inflammation in COPD. It was really great speaking with you today.

Dr. Maselli:
Thank you so much for having me.

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