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

Next Steps in COPD Care: Exploring Biologics for Frequent Exacerbators

Announcer:
You're listening to *Deep Breaths: Updates from CHEST* on ReachMD. This program is produced in partnership with the American College of Chest Physicians and is sponsored by Sanofi and Regeneron. And now, here's your host, Dr. Diego Maselli.

Dr. Maselli:
Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Diego Maselli, a Professor of Medicine at the Long School of Medicine at UT Health San Antonio. And today, we're exploring the emerging role of biologics in COPD care.

Joining me in this discussion is Dr. Stephanie Christenson, who is an Associate Professor at the University of California in San Francisco. She's part of the faculty of the Division of Pulmonary Critical Care, Allergy, and Sleep Medicine. She attends the pulmonary consult services and the Pulmonary Clinic.

Stephanie, thank you so much for joining us today.

Dr. Christenson:
Great to see you.

Dr. Maselli:
Great to see you, too. So, today we're going to be talking about COPD and we're going to be focusing on advanced therapies. As we know, COPD exacerbations happen to a lot of our patients. These are important events in their lives because these exacerbations have been associated with worse quality of life and lung function decline, and very importantly, these observations are the most important risk for future events and future exacerbations. Trying to prevent these events has become really important.

Particularly, those events that lead to hospitalizations are very serious. The data shows that one hospitalization occurs for COPD every minute in the United States. The numbers are, to me, very incredible. These events appear to be very frequent, so there's a lot of interest in trying to prevent these events.

Stephanie, how do you think these exacerbations and how these events affect our patients has really changed the landscape for COPD? And why is there such an interest now in biologics for COPD?

Dr. Christenson:
Well, I think you kind of hit the nail on the head when you were talking about there being an exacerbation every minute, and severe exacerbations, so those that cause hospitalization or emergency room visits, really increase risk of mortality and increase risk of cardiovascular events. So, they're really horrible for you, and they're really frequently occurring.

And we've had inhaled therapies around for many years, right? And we combine them, and most recently, we have triple therapies where we combine all three of our most common ones—the long-acting beta agonist, the long-acting antimuscarinic, and the inhaled corticosteroid—into one drug. Actually, if we give those drugs, and depending on if they have type 2 inflammation or not, if we give either that combination or a dual—so long-acting beta agonist and long-acting antimuscarinic—we can decrease exacerbations and decrease their frequency and decrease their severity. But like you said, they're still super frequent, and we still have a lot of people exacerbating despite those therapies.

We see that in these very large trials of inhaled therapies where we can see a reduction, but we still have a lot going on with these patients. So, you really still see a lot of patients who are still suffering, both exacerbations—or I would say one of the major issues for

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my patients, and I'm sure yours as well, is their symptom burden. So, they've got a lot of chronic cough, or they have a lot of dyspnea, or they can't do the things that they want to do, like interact as well with their peers or play with their grandkids. Or I live in California, so a lot of them used to be hiking along our beaches and our mountains and they can't do those things like they used to be able to.

What do you think? Are you seeing kind of a similar thing—that we've got a lot of these drugs, but we've still got a lot of unmet need?

Dr. Maselli:
Definitely. You mentioned triple therapy as really a gold standard for some of our patients that have frequent or recurrent exacerbations, and these therapies absolutely work well, but an important proportion of these patients have still exacerbations despite triple therapy.

You mentioned large scale studies that looked at this, and it's important to mention that in these group of patients, they were compliant with these therapies. The investigators called the patients and the nurses called the patients, and despite that, around 50 percent of the patients had at least one exacerbation during the trial. So these events happened even in those that were compliant with triple therapy.

So, you mentioned a little bit before about that type 2 inflammation and how that is becoming more important and important. How are you testing for type 2 inflammation in your COPD patients?

Dr. Christenson:
I think similar to what we do in asthma, we're using blood eosinophils really to test for type 2 inflammation. And before, we thought about things like biologics. We've been using blood eosinophils to test for type 2 inflammation. So thinking about allergic inflammation, response to parasites and helmids, and the classic inflammation and asthma.

But we can see elevated blood eosinophil levels in up to, depending on which patient population we're talking about—an exacerbator population or just COPD overall—20 to 40 percent of our patients have elevated eosinophil counts. So that is certainly important. And what it's really measuring, like I said, is allergic inflammation. And some of the things that we think about there are eosinophil, THT helper type 2 cells, ILCT cells, and the cytokines, which become important when we're talking about things like biologics. IL-4, IL-13 and IL-5 are the key cytokines. Although, upstream of those are some of the alarmins where if you hit the epithelium or other cells with a certain stimuli, like an allergen or smoking, then you release these alarmins that lead to this cascade, and those would be IL-33, TSLP, and IL-25.

So, there's a lot going into the type 2 response. But in general, once we find a type 2 response, we know that we have ways to treat that —both inhaled corticosteroids, so steroids can treat the type 2 response, but there can still be type 2 response left, even after we treat with inhaled steroids.

Dr. Maselli:
This is a very important point—to understand the pathways—and we've learned so much from the severe asthma space that we can now borrow some of these concepts into COPD.

The GINA guidelines have recommended that we should check eosinophils on our patients with severe asthma up to three times. I don't know if there's a lot of guidance yet from the GOLD report—the 2025 report does not necessarily mention how often we should measure our eosinophils. They recommend measuring eosinophils. What's your practice with regards to how often? Or do you do trends? What do you do in COPD?

Dr. Christenson:
I take note from the asthma space as well, because I think eosinophils can be decreased if, let's say, you measure them only at the time of the COPD exacerbation after a patient has gotten oral steroids. Well, that might have decreased their blood eosinophils.

But also, there's a lot of variation. Even just during the day, there's diurnal variation, so I will oftentimes check multiple times because I'm really trying to understand who's got evidence of at least some type 2 inflammation. One of the reasons for that, too, is that —and this is what GOLD suggests as well—the patients who have eosinophils less than 100 and are consistently less than 100, even when they're not on inhaled steroids, are probably the patients who are not going to respond particularly well to medications targeting type 2 inflammation. And so that is mostly based off of inhaled corticosteroid studies. But there's quite a bit of data for that, which is why they've put it in their recommendations.

Dr. Maselli:
Yeah, that makes sense. So, in asthma, we've learned that high eosinophil count may actually be predictive of future exacerbations and patients with that eosinophilic phenotype—or eosinophilic endotype, as some people will describe it—have a higher risk for future poor outcomes. Do you see that translating to the COPD space?

Dr. Christenson:

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Yeah. I think it does translate to the COPD space. I know that there's been some studies showing that eosinophils are predictive of future exacerbations. Although, still, the best predictor is still prior exacerbations. And I would say that COPD is a very heterogeneous disease, and so is asthma, but in particular, COPD—in regards to type 2 inflammation—is pretty heterogeneous.

So if you're using these drugs, you really do want to make sure people have type 2 inflammation—so either biologics or inhaled steroids. I think there can be risk of pneumonia in using inhaled steroids. It's a small, but pretty relevant risk. So we want to make sure we're not using, in particular, inhaled steroids if it's in a patient who may not be the best candidate for one, because we don't think they're going to respond and maybe it would increase their risk.

So that is certainly something I'm consistently thinking about. So there is a little bit of data to answer your question on eosinophils predicting risk, but there's a lot of heterogeneity there. So it's so important to really be looking at eosinophils and looking for elevated counts to help guide our treatment.

Dr. Maselli:
Yes, I feel like the eosinophilic phenotype is definitely more common in the severe asthmatics than in our patients with frequent exacerbations in COPD. I agree with you.

Dr. Christenson:
Absolutely.

Dr. Maselli:
For those just joining us, this is *Deep Breaths: Updates from CHEST* on ReachMD.

Stephanie, we have some biologics that actually can target potentially type 2 inflammation in COPD. How do you approach all your patients who may be candidates for a biologic in COPD? Who are the patients that you feel like could benefit from these medications?

Dr. Christenson:
So I'm really thinking about it in anybody who is that exacerbation-prone phenotype, meaning that they've had two moderates, or ones that require oral steroids, or any kind of treatment in a healthcare utilization. So they're seeing their physician because they've got an increase in symptoms beyond their day-to-day variation, or they've got a severe exacerbation, which it depends on which study you look at as to what that means. But I would say anytime they're going to the emergency room or going and getting hospitalized, I'm really thinking about, "Hey, are you on all of your appropriate medications? Are you taking those medications correctly?" We know that for anybody who takes an inhaled therapy, there's a lot of room to not use those correctly—either not using them every day, or not having an appropriate inhaler technique. I'm certainly thinking about other things that could potentially help my patients, like pulmonary rehab.

But really, in this patient population, who continues to exacerbate on otherwise maximum medical therapy, is where I'm like, "Hey, would you be a candidate for a biologic?" And that's when I start looking at their eosinophil counts, and I'll look both at the ones I'm getting right at that time, but I might actually go back because many of our patients have eosinophil counts from prior.

So I'm really looking across the board no matter what other symptoms or aspects you have to your COPD. So patients sometimes have chronic bronchitis and/or emphysema, and I think we are seeing some inkling that these drugs might work across groups as long as there's evidence of type 2 inflammation. So I'm not just saying, "Hey, you have to fall into a specific category." What about you?

Dr. Maselli:
Yes, I agree with you. I think with patients that have frequent exacerbations, particularly those who have had hospitalizations with compliance to triple therapy, we definitely start to have a red flag of sorts. And say we have to do some interventions if they haven't been compliant and are still not responding, then we do have options. And if they have that eosinophilic phenotype, then we may consider a biologic in that case.

Dr. Christenson:
Yes.

Dr. Maselli:
When a patient has active smoking, does that change your approach? I know you always focus on smoking cessation, of course, and talking to them as much as you can. But in the interim, while they're trying to stop smoking, do you proceed with a biologic? What is your opinion about that? I know that's a controversial area.

Dr. Christenson:
I really look at smoking as its own disease. It's really hard to stop smoking, and there's a lot of other things that are in play with smoking, right? Some people have been doing it for many years and have addiction-like properties. Some people could have depression or other

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reasons that it's hard to quit smoking. In fact, that's a major comorbidity for COPD.

But I, in general, think of it as its own disease, and so I'm always trying to work on smoking cessation even before patients are ready—either working with them on pharmacotherapy or referring them to programs to help with that. But I would say that at least the data for biologics that are currently approved is that they do work in current smokers. And even if somebody tries to stop smoking, or does actually get to stop smoking, there's also risk of starting smoking again, and I don't think that people should be excluded from our therapies just because they have this habit. I mean, we don't withhold cardiovascular drugs from patients because they eat hamburgers or smoke.

So I don't think it's appropriate to try to withhold a drug if we think it might help in our patients. And maybe it will get them under good enough control or could help with their control enough where they might feel more comfortable stopping smoking since we know that sometimes it increases their symptoms in the short term.

Dr. Maselli:
I think you have to proceed most of the time with therapy. I agree that smoking cessation is one of the most difficult things a patient may encounter with COPD. So we are always aggressive and supportive with regards to medications and counseling and many other things and insisting that they stop smoking as much as we can. But we don't want to withhold these therapies that potentially could be beneficial for them.

Another question I has for you is in our asthmatics, when we're trying to treat them, sometimes they have some concerns about if the medication is safe and effective. Some patients have raised some concerns about it. In the asthma space, most of the time, everyone is eager to have that treatment given. Our COPD patients are a little bit older, maybe a little bit different, and I know you've treated several patients with COPD already with biologics. Have they raised any specific concerns? And if so, how do you approach those concerns?

Dr. Christenson:
I mean there's always concerns about an injectable, especially, as you were saying, in an older patient population. I think how we address that is, we should try to show the patient what an injectable looks like and how you would use it and make sure that they are comfortable with it. And working at an academic center means that we have nurses who are very good at helping teach those things. But I think some of our specialty pharmacies are becoming more and more adept at using these biologics in our airway disease patients and are certainly already very comfortable teaching in rheumatologic diseases and many other diseases, so they have a lot of experience.

So I try to handhold a little bit as far as really teaching them what this looks like. And we go through kind of the risks and that in general, the safety profiles have been very similar to what we've seen in other diseases, and that we have had approval for many of these drug classes for many years in other diseases. But we are certainly there if there is any major concerns.

What about you? What are you telling people?

Dr. Maselli:
Very similar to you, I think, because we have the experience with severe asthma in the past. We have used our respiratory therapists and our pharmacists, to provide a lot of education and reassurance about how to use the devices and how to use these injectables.

And as you mentioned before, a lot of people are using it in different specialties: dermatology, the diabetes space, and we use it also in our pulmonary diseases already. So there's a lot of familiarity, and fortunately, we've had some good experience with it and patients seem to be tolerating and okay so far.

Dr. Christenson:
Yeah. And I think one of the important points is that, first of all, level-setting with our patients that these patients already have fixed defects and maybe they've been deconditioned for quite some time, and so not necessarily a safety, but what kind of response do we expect? And that I want to give it a little time to make sure things are working, like making sure somebody gets through an exacerbation season like the winter, when we think that they're more likely to exacerbate. And it will be great if these drugs help with any of their symptoms, but they were certainly powered and their primary outcomes were based on exacerbation.

So, that's what we're trying to see. Are they either having decreased numbers of exacerbations, or decreased severity of their exacerbations? And so I do want to try to make sure patients get to a point where we can see maybe if that's a response.

But I will say I don't have to keep these drugs going indefinitely if they're not working. And I think that is something that patients ask me about—"Once I start it, can I ever stop?" I'm like, "Well, if it's really working for you, then you may not want to. But as far as if something's not working for you, then yes, we don't have to just keep going indefinitely on a drug if it's not working."

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Because COPD is a very heterogeneous disease, as we said. We're in the age of precision medicine, and we're hopeful that one of these drugs works.

So, I think that that's another point that I like to raise with patients—the expectations of what we might see in a biologic, that we are hopeful that it decreases your exacerbations and maybe helps you start feeling better, but that just like anything else, it's not a magic bullet. And we want to make sure that we're doing this while also keeping them on their current therapies and really making sure they're getting pulmonary rehabilitation, they're getting appropriate vaccinations, and we're still thinking about smoking cessation. So I do like to make sure patients understand that it's still within the realm of we want to treat them for their COPD as a whole.

So, Diego, what about you? What do you think of as your key takeaways and final thoughts about giving patients biologics in the COPD space?

Dr. Maselli:
This is an incredibly exciting time for COPD. I agree with you that we have these fantastic new tools, but we have to, like you mentioned before, be holistic about how we approach our patients with COPD. We still have to remember that we have all these preventative measures that we have—the vaccines, having them use the medications regularly, the compliance, and other tools that we have available in the bronchial valves. And we mentioned nutrition, talking about comorbid conditions and smoking cessation, like you mentioned before.

Well, this was an incredibly informative discussion. I'd like to thank my guest, Dr. Stephanie Christenson, for joining me today to share her insights on how biologics can fit into our COPD management.

Dr. Christenson:
Yeah. Thanks for having me.

Dr. Maselli:
Thank you so much, Stephanie, for being with us today.

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