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Unmet Needs and Emerging Evidence in Severe Asthma: Two-Year Data on an Ultra-Long-Acting Biologic

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And now, here's your host, Dr. Donna Gardner.

Dr. Gardner:
Welcome to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Donna Gardner, Chief Research and Programs Officer at Allergy & Asthma Network in Fairfax, Virginia. Today, we'll be discussing persistent unmet needs and challenges in the management of severe asthma, along with the emerging two-year evidence for an ultra-long-acting biologic dosed once every six months, and considerations for treatment decision-making.

Joining me for this conversation is Dr. Nicola Hanania, Brown Foundation Professor of Medicine and the Director of Airways Clinical Research Center at Baylor College of Medicine. He is also Chief of the Section of Pulmonary, Critical Care, and Sleep Medicine at Ben Taub Hospital in Houston, Texas. Dr. Hanania, thanks so much for being here today.

Dr. Hanania:
It's great to join you, Dr. Gardner, and thank you for having me. I look forward to a fruitful discussion.

Dr. Gardner:
All right, so let's jump right in. Nic, even with more biologic options available, we're still seeing patients with severe asthma who aren't achieving adequate control. From your perspective, what are the biggest unmet needs, and why do you think there are gaps between guideline recommendations and what happens in real-world practice?

Dr. Hanania:
Well, thank you for the question. It is indeed troubling to see that about 50 to 60 percent of patients remain uncontrolled, despite the fact that we have good treatments for asthma. But many of these continue to have exacerbations despite being on their controller inhalers, which are important. And yet only 20 percent of these patients in what we call GINA group 5, who already are on optimized standard-of-care inhalers, receive what has now become a really important intervention, and that's biologic therapy.

And there are multiple gaps with this, including health system gaps, delay in getting authorization and approval, patient's hesitation of going on injection, frequency of administration of these biologics, which sometimes scares the patient away, and lack of infrastructure in the healthcare system. There's also a delay in specialist referral, because we know that biologics are prescribed by specialists. So it's multifactorial, why we are seeing delay in initiation of biologics. And we continue to see these patients struggle, unfortunately, with their asthma.

Dr. Gardner:
As we've learned more about persistent type 2 inflammation and its role in severe asthma, how has that changed the way you think about long-term treatment goals and timing of biologics initiation?

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Dr. Hanania:
Well, DeDe, you probably remember too that when we approached asthma in a different way in the past, we thought this was a one-phase, one-size-fits-all disease, and inhalers will do the trick. But now, as we know more about not only the phenotypes, but the endotypes or mechanisms of asthma, we've learned that the majority of asthmatics—70 percent of them—have what we call type 2 inflammation. And it is actually not hard to pinpoint this type of inflammation by measuring biomarkers like blood eosinophils and exhaled nitric oxide.

But also, allergic asthma is one type of asthma that is characterized by type 2 inflammation. So, as we learn more about type 2 inflammation, we learn about how to target it. Obviously, inhaled corticosteroids remain the mainstay for treatment for these patients, and certainly, increasing the dose of inhaled steroids may help. But science has shown us that doubling inhaled steroids, even quadrupling inhaled steroids, may sometimes not do the job. In fact, it exposes the patient to higher systemic effects of these inhaled steroids.

So that's when we started thinking outside the box. What can we do for this type 2 inflammation? How can we stop it? Well, we went to the root cause, and what drives this are inflammatory cells—eosinophils, but also cytokines. These cytokines are important, and not only important for bringing these eosinophils to the airway. Interleukin 5, for example, is an important cytokine that has been known for many years, but now we can target it with biologics. Other interleukins, like four and thirteen, but also epithelial cytokines or what we call alarmins, are very important. So the evolving field in type 2 inflammation has really shown us that we need to go to a more precise approach for the treatment of asthma—not just this one-size-fits-all approach.

The timing of initiation of biologics is so important. Actually, there's been several studies, including some of ours, that show that delay in initiation may be associated with poor outcomes and, indeed, increased healthcare utilization. We just presented some data at the ERS meeting, and when we look at the real world, delaying initiation has a cost implication, but also a healthcare utilization implication.

But on a disease basis, we believe that if inflammation remains unchecked, it can actually cause progression of the disease and maybe changes in the airway, with remodeling. So it's very essential, once we find or identify patients who are candidates for a biologic, to not to waste more time and try to get treatment, as quickly as possible—obviously, as feasibly as possible—because sometimes it takes time for us to get approvals, prior authorization, and shared decision-making with the patient. But it is very important not to delay the start of biologics.

Dr. Gardner:
Despite advances in biologic therapy, challenges remain with biologic initiation and long-term treatment persistence. What barriers do you continue to see in clinical practice?

Dr. Hanania:
Unfortunately, it is estimated that only 20 percent of patients who—when you look at their profile, exacerbation history, and biomarkers—are eligible for a biologic, receive it.

There is definitely lifestyle modification needed for managing asthma. And certainly, patients may prefer to hold off going on a biologic, and they may have hesitation. Many of them have their own work, and the frequency and mode of administration does not appeal to them. They don't like injections. They don't want to inject themselves every month, and they try to avoid it. Fear of injection is still a real concern, although nowadays, with the ease of injecting these biologics and educating the patient, we may alleviate some of this fear.

But also, healthcare providers aren't really acquainted with all these biologics. Their referral to specialty care remains low in these high-risk patients. And, with all my respect to primary care colleagues, we're not getting these patients with red flags. Those who exacerbate frequently, those who need oral steroids more than twice a year, those who continue to have symptoms, those are the ones that we really need to see in specialty care, because that's where biologics are prescribed.

So I think it's a multifactorial reason why we're seeing delay in initiation of biologics. I think, as we understand this disease more and more, now we have other offerings, where we can give longer-acting agents that may not need as frequent administration, and that may help alleviate some of the concerns that the patients have.

Dr. Gardner:
For those just tuning in, you're listening to *Deep Breaths: Updates from CHEST* on ReachMD. I'm Dr. Donna Gardner, and I'm speaking with Dr. Nicola Hanania about persistent unmet needs in severe asthma and emerging clinical evidence.

Nic, we've discussed some of the ongoing challenges in severe asthma management, so let's turn now to depemokimab. What should clinicians know about the ultra-long-acting anti-IL-5 as one option of a targeted approach before we discuss the clinical data?

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Dr. Hanania:
Depemokimab is one of the new biologics that has been approved now for severe eosinophilic asthma. And depemokimab is an anti-IL-5, so it does target interleukin 5, a very important cytokine. But it is dosed every six months, creating a regimen, especially for patients who do not want be given injections or taking injections frequently. And that's the value of depemokimab, in a way. It is the only biologic approved now for asthma that is dosed every six months—so twice a year, basically.

I mentioned earlier that many patients are hesitant to get injections every month or every two weeks. And actually, a substantial number of patients who start on a biologic end up stopping. About 50 to 55 percent of patients discontinue their treatment within the first year. So it's a real fact that adherence to even these important drugs is not 100 percent. And part of the reason—not all of the reason—is that patients have their own life. They don't want to be doing this every two weeks or one month. They travel a lot. They cannot keep up with the need for a monthly or every two-week injection.

So the way we're looking at it is, where can we simplify their life? They already have complicated lives with their asthma, unfortunately. They have uncontrolled disease. Often, they have to miss work because of their asthma. They end up being in the emergency room. Can we actually improve the way we deliver some of these biologics to them? And that's the way things are going. We're looking at if we can simplify things for them.

Dr. Gardner:
So with all this in mind, can you walk us through the key findings from the SWIFT 1 and 2 and AGILE clinical trials, and what those results may mean for clinicians like yourself managing patients with severe asthma?

Dr. Hanania:
SWIFT 1 and 2 both are replicate, phase three, randomized double-blind placebo-controlled trials. They were multicenter international studies. And the main purpose of SWIFT 1 and 2 was to investigate efficacy and safety of depemokimab injection given twice a year over 52 weeks in a large population of patients with severe asthma who have history of exacerbations—two or more in the past twelve months. They were 12 years of age and older. They had to show eosinophilic inflammation reflected on by baseline blood eosinophil of more than 150 cells per cubic liter on screening, or more than 300 cells per cubic liter in the past 12 months prior to visit one.

They could have any asthma control scores. Some of these patients had asthma control scores that were within normal. Others had worse asthma control. They all had to show some airway obstruction, with an FEV1 less than 80 percent in adults and less than 90 percent in those aged 12 to 17. And of course, they all had to be on baseline medium-to-high dose inhaled steroids for at least three months in addition to another controller, usually, a long-acting beta agonist.

And these patients were randomized to either the depemokimab injection every six months or placebo in a 2:1 ratio. And the main endpoint of these two important studies were the annualized rate of exacerbation over the one year of the study. Of course, there were several secondary endpoints.

And the bottom line is that, in these studies, the main endpoint—which is the annualized rate of exacerbation over 52 weeks—was met with a reduction by 54 percent compared to placebo. It was met in both studies. There was also an important improvement in or reduction in exacerbation requiring hospitalization or emergency department visits as well. And importantly, safety was confirmed in these two large trials of depemokimab compared to placebo over the one year.

And then these patients were followed for another year in the AGILE open-label extension study, where patients who were on placebo were put on open-label depemokimab. Those on depemokimab continued. So we have an extra year of follow-up looking at long-term safety.

And this is an important design, in a way, to look at safety over two years. It’s basically an extension of the randomized controlled trial, but also looks at other potential issues, like immunogenicity. And the good news is that, in the AGILE open-label extension, this study showed extension of what was shown in the clinical trial: reduced exacerbation over an extra year of follow-up, and maintenance of the safety of this drug. The safety was pretty well confirmed in these trials. No significant safety issues were brought up in this study. There were several sub-analyses of subgroups in these patients, and I think that shows that this drug may work in the larger population of severe asthma patients with eosinophilic inflammation who continue to have exacerbations.

Dr. Gardner:
Thanks for sharing all of that. Those are really important findings for our patients. Well, we're almost out of time for today, but before we wrap up, Nic, what factors should guide treatment conversations and shared decision-making with patients who may be candidates for biologic therapy?

Dr. Hanania:

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I'm glad you brought it up, because shared decision-making is important. And I know you've been very involved with patients and families, so thank you for all that you do and the extra work that you put in.

But I think shared decision-making is absolutely important, because patients who you start on a biologic always have questions. It's not a one-way highway. It's a conversation that we have to have. Patients have choices. They need to help us. We have choices, too, and there are multiple biologics available that may work. But having the patient's input on the number of doses of injections, and how frequent the patient wants it.

But we also talk about other things, like the safety of the drug, what is it for them, when they feel better, and how long are they going to be on it. And of course, they are always worried about cost and coverage. And so we work with them and with their payers and insurance to make sure we pick the right biologic for them.

So I think it's not black and white. And we have to spend some time with each patient so that they can remain adherent. Otherwise, as I mentioned earlier, many of these patients will drop off—even if you get them approval—during the first year of starting the biologic. Only 21 percent of patients consistently adhere to therapy, based on a recent publication. And unfortunately, more than half of these patients who are started on a biologic may stop in the first year.

Dr. Gardner:
It sure is important. Patients do experience some different reasons or barriers that contribute to why they aren't adherent, and sometimes, we see or hear from patients that they are extending things longer than they should be. So making sure that we have the right patient with the right treatment at the right time is extremely important, and for them to be part of the conversation, like you said. Making that shared decision-making decision at the end of the day is really important for them.

Dr. Hanania:
Absolutely right. Yes. Well said.

Dr. Gardner:
And with that, we come to the end of today's program. I'd like to thank Nic for joining me today in discussing persistent unmet needs in severe asthma, emerging clinical evidence, and considerations for treatment decision-making. Nic, it's been a pleasure.

Dr. Hanania:
Oh, it's a pleasure, and thank you for having me.

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