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Uncontrolled Moderate-to-Severe-Asthma: Latest Data from the Floor of CHEST 2018

Announcer:
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Your host is Dr. Jennifer Caudle.

Dr Caudle:
This is CME on ReachMD and I'm your host, Dr. Jennifer Caudle, joining you live from the CHEST Annual Meeting in San Antonio. Before we dive into our discussions from the CHEST Conference, I'd like to welcome Dr. Mario Castro, whom we spoke with after the conference about the data presented there.

Dr. Castro is a professor of Pulmonary and Critical Care Medicine at the Washington University School of Medicine in St. Louis, Missouri.

Dr. Castro, thank you for joining me today.

Dr. Castro:
Well, thank you for having me.

Dr. Caudle:
So, Dr. Castro, the treatment of severe asthma has changed significantly in the last few years because of the approval of new biologic therapies. We were able to discuss some new data from phase 3 trials of 3 of these biologics at the CHEST conference. But before we get to that, can you review the biologics with us?

Dr. Castro:
Thank you. It's definitely an exciting time for us providers that are treating asthma patients because we now have these biologic therapies which are quite effective by selecting patients that are appropriate for them with a very acceptable side effect profile. So, we certainly have a lot of experience with an anti-IgE monoclonal antibody, which is omalizumab, and in that experience we have demonstrated previously that this helps us stabilize our patients that have significant allergic asthma, severe allergic asthma, and in those individuals, we see that omalizumab reduces their exacerbation rates by approximately 25% and helps stabilize their disease. But in addition, we now have 3 anti-IL-5 therapies which help us in patients who have severe eosinophilic asthma, and typically we're talking about eosinophil levels greater than 300. These 3 anti-IL-5 agents have all shown to be very powerful in terms of reducing exacerbations, but surprisingly, we're also seeing an improvement in lung function with these agents. Now, lastly, we have a new agent that attacks another pathway that inhibits the IL-4 receptor, and by blocking that receptor actually inhibits both IL-4 and 13, 2 of the T2 cytokines that are key in pathogenesis of asthma. And these recent results demonstrate that there is significant reduction in exacerbations, improvement in lung function, and then lastly, in the trial in oral steroid-dependent patients, demonstrating that about

half of our patients that are on chronic oral steroids are able to get off of this chronic oral steroid medication with the use of an anti-IL-4 receptor, such as dupilumab.

Now, in terms of dupilumab side effects, the main ones we saw were injection site reactions, and that occurred in up to about 14% of patients. Otherwise, it is very well tolerated. We did see in a subset of patients some peripheral blood eosinophilia. That tended to be transient and resolved over time. So this does allow us to have now a new agent that tackles a different group of patients than the interleukin-5 inhibitors.

In my own practice, I feel that dupilumab is going to offer some opportunity to treat those patients that may not have eosinophilic asthma but have T2-driven disease as demonstrated by an increase in their fractional exhaled nitric oxide levels, or FeNO levels. We noted in this study that those patients that had a FeNO level greater than 25 parts per billion actually responded quite well to dupilumab, so this now offers another subgroup of patients that we can treat with a biologic.

Dr. Caudle:
And what factors do you consider when selecting initial therapy for an individual patient?

Dr. Castro:
That's a great question, and I do think that we think about shared decision-making with our patients, and we need to think about what are their individual preferences. We provide the knowledge behind kind of how these agents work, but patients need to participate in that decision-making, and one of the key things I think, as I mentioned earlier, is the mode of administration. Some patients prefer a subcutaneous injection, and therefore, I'm going to use an anti-IL-5, I'm going to use mepolizumab, or I'm going to use benralizumab. If they use an IL-4 receptor, I'm going to use dupilumab in that patient. If they need weight-based dosing and do not mind intravenous therapy, then I'll use reslizumab in that particular patient. So that's where I integrate patient decision-making or shared decision-making into considering what agent I will use initially in an individual patient.

Now, further, we need to use our biomarkers to help us make this decision. So, when we think about those patients that have eosinophilic asthma, an eosinophil level greater than 300 for benralizumab and for mepolizumab and greater than 400 for reslizumab, we want to make sure that you measure circulating eosinophil counts and the CBC with differential, and this allows you to select that eosinophilic patient.

Now, what about the patient that has severe allergic asthma? Well, I'm going to be measuring their IgE level and looking at results from allergy skin testing or from their ImmunoCAP from their allergic-specific IgE, and so that allows me to identify a patient that is sensitized that may respond to an anti-IgE therapy.

Now, the last group of patients are those patients that have an uncontrolled disease that we believe may be mediated by one of these T2 cytokines, IL-4 and -13. And so patients that have elevation in their eosinophil counts respond better to dupilumab in general, and certainly, when we see the higher eosinophil count, they respond better, but also, these patients that have elevated FeNO levels, we know that they'll respond very well to dupilumab.

So those are the 3 biomarkers that I use to really select the appropriate initial therapy for a patient that I'm considering for a biologic therapy.

Dr. Caudle:
Dr. Castro, let's go on and discuss some of the phase 3 data on dupilumab that was presented at the CHEST meeting. This was an analysis from a study called the LIBERTY ASTHMA QUEST study. What can you tell us about this study?

Dr. Castro:
So, in the phase 3 QUEST study, we evaluated the effect of dupilumab either at 200 mg or 300 mg given every 2 weeks subcutaneously. What we found in the overall QUEST study is that patients that were treated with either of the doses of dupilumab, either the 200 or the 300 mg dose, that there was a 46% to 48% reduction in exacerbations, and this was accompanied by approximately a 320 to 340 ml improvement in their FEV1. This was approximately 130, 140 above placebo.

We noted the effect on lung function was very quick. It occurred even after the first injection. There was a significant improvement in FEV1 just 2 weeks later after that first injection. In addition, we found that the use of biomarkers, as mentioned earlier, was quite helpful in selecting those patients that would proximally respond to dupilumab. We found in those patients that were greater than 300 cells per microliter with their blood eosinophil count, that these patients actually had somewhere around a 66% to 67% reduction in exacerbations. Furthermore, in the use of another biomarker—as we mentioned the FeNO—if you had a FeNO level greater than 25 parts per billion, then you had a reduction in exacerbations somewhere around 61% to 65%.

Dr. Caudle:

So, what did you find when you looked at the adolescents enrolled in the study?

Dr. Castro:
So, in the recent study that was just released at the CHEST conference, we looked at a subset of patients that were treated with dupilumab in the adolescent age range, so this is in the age range of 12 to 17 years of age. Now, this was a smaller subset analysis of approximately 107 adolescents, and what we found was that these patients, when treated with dupilumab, had about a 46% reduction in exacerbations in the patients that were treated with the 200 mg subq dose every 2 weeks. Now, when we looked at the improvement in lung function, again there were significant improvements in the lung function from baseline in adolescents treated with the 200 mg and the 300 mg dose, so there was approximately a 270 to 360 ml improvement in FEV1. The side effects in the adolescents were very similar to what we had seen in adults in that the most common adverse reaction was pain at the injection site or injection site reactions.

So this data, I think, is exciting because now we know that this new class of monoclonal antibodies will help us treat even adolescents with severe, uncontrolled asthma.

Dr. Caudle:
And finally, what would you say are the most important takeaway messages you'd like to share with our audience today?

Dr. Castro:
Well, I think, as I mentioned, this is an exciting time for us as asthma specialists in treating this disease, that we now have the tools, the biomarkers to help select the appropriate set of patients that have either eosinophilic asthma or allergic atopic asthma or a T2-driven disease that allows to select an appropriate biologic therapy to help control their disease much better than we've ever before and help us avoid the side effects that we've seen from chronic oral steroid exposure. So I think we really need to kind of rethink how we evaluate these patients in our clinical practice. We need to certainly think about how many courses of steroids did this patient get over the last year, and are there things that we can help control their disease better? And so, I think with this information that we just shared, I think it allows us to kind of think there may be a specific therapy that we could use for these patients to get their disease under control with much greater efficacy and acceptable safety profile.

Dr. Caudle:
Dr. Castro, thank you for taking the time to discuss new treatments and the details of this promising trial.

Dr. Castro:
Thank you.

Dr. Caudle:
For those just joining us, this is CME on ReachMD. I'm Dr. Jennifer Caudle, your host, and I'm at the CHEST Annual Meeting in San Antonio, TX to discuss the latest data with pulmonary experts.

Joining me now is Dr. Nick Hanania, Associate Professor of Medicine, member of the Division of Pulmonary Critical Care and Sleep Medicine, and the Director of the Airways Clinical Research Center at Baylor College of Medicine in Houston, Texas.

Dr. Hanania, welcome to the program.

Dr. Hanania:
Thanks, Dr. Caudle, glad to be here.

Dr. Caudle:
Well, I'm very happy that you're here. So, Dr. Hanania, earlier you presented secondary analysis from the pivotal omalizumab phase 3 trials. Why don't we begin by talking about those trials? How were those studies designed?

Dr. Hanania:
So those trials on omalizumab were done several years ago, and actually, those are the pivotal trials that got this anti-IgE biologic approved for patients with moderate to severe allergic asthma. They were designed to look at whether adding an anti-IgE to patients with allergic asthma who are uncontrolled can improve or reduce the risk of exacerbations. They were specifically designed to include patients with allergic phenotype, meaning these patients had to have some kind of perennial allergy, they had to have moderate to severe asthma by lung function but also by symptoms, and they had to be on at least inhaled corticosteroids at baseline. Some of these patients, although not all of them, were also on additional controller medications such as long-acting bronchodilators. They had 2 phases, a stable phase where they were 16 weeks, and that's the phase that we looked at in this analysis where they were kept on the same dose of inhaled corticosteroids that were on at the beginning of the study. Now, the second phase, which is not part of our investigation here, was a step-down phase where they tried to get the inhaled steroid dose lowered. And the main purpose of these studies—they were 2 very similarly designed—is to look at exacerbation over the period of time of this study. Both studies achieved the

primary goal. And that's how this drug was approved initially for that population of patients.

Dr. Caudle:
Thank you for that. And I'm going to ask you a question that touches a little bit on what you already talked about, but maybe to reiterate for us, the data you just presented was a new post-hoc analysis combining data from the 2 trials. What outcomes were you looking at, and why was it done?

Dr. Hanania:
Well, the reason we went back and looked at these data or revisited them is we were interested to look at lung function change. As a biologic, omalizumab has a very good effect in reducing exacerbation. That we know and we knew from multiple studies published. We recently looked at data from real-life studies with the drug, and we actually showed improvement in lung function as well. Now, this drug is not a bronchodilator, so it's not expected to show a dramatic change in lung function, but we were interested to see if in the first 16 weeks or the stable phase of these pivotal trials whether lung function improvement is different than in patients receiving placebo. It was a placebo-controlled trial. But more importantly, we wanted to see if there are any predictors that predict response in lung function. For a clinician like myself, I would like to know when a patient comes to me if I put the patient on omalizumab, would I see lung function improvement? If so, are there patients that may show better lung function improvement than others? Are there any biomarkers that I can use maybe that can help me predict response to lung function? So that's the purpose of this post-hoc analysis.

Dr. Caudle:
No, those endpoints make perfect sense from a clinical standpoint, absolutely. And again, you talked about this as well. Let's go again over some of the results that you found, what the research showed, if you can kind of go through that again for us, please.

Dr. Hanania:
Yes, so we looked at several parameters. Our outcome measures, as I mentioned, was lung function, and you can measure lung function looking at FEV_1, which is the forced expiratory volume in 1 second. We looked at the forced vital capacity, another important physiologic parameter. And we also looked at the percent predicted based on age and height and sex of the patient, change in the percent predicted FEV_1, so these were the 3 physiologic parameters we looked at. We looked at dose over the 16-week treatment period, and we compared the treatment versus the placebo arm. Our first finding was a significant improvement in lung function as early as 4 weeks with omalizumab versus placebo in all these physiologic parameters, but a sustained improvement over 16 weeks, so the improvement in lung function persisted. That really confirms the short-term effect on lung function. That actually corresponds to what we've seen in larger trials on the longer-term basis.

But, also, we dissected the data further. We looked at subgroups. We looked at parameters that may predict response. And we found that patients who have high blood eosinophils at baseline tend to have better lung function improvement. We looked at different cutoffs. We looked at cutoff of 150 cells per microliter. We looked at 300 cells per microliter. The higher the blood eosinophils at baseline, the better effect in lung function improvement. We also looked at whether bronchodilator reversibility at baseline, which is measured by giving albuterol and looking at lung function change—and again, that also correlated with better improvement with lung function with omalizumab. And the final thing we looked at is how severe was lung function impairment at baseline. Based on a cutoff of 65% of predicted, we found that patients who have more severe lung function impairment like FEV_1 less than 65% had actually more pronounced improvement in lung function.

So these are the 3 parameters among our analysis that predicted response in lung function, and these are important findings too, even though the studies were published many years ago, but I think looking at this lung function improvement is important.

Dr. Caudle:
Absolutely. And finally, I think the question that many of us also want to have answered is how these results you feel will affect our clinical practice, and really, what should clinicians take away from this research?

Dr. Hanania:
Two things that I would take away from this research, one is, when I use a biologic, I would like to know what happens to the whole patient. Obviously, exacerbations are important endpoints, and we know that these drugs, just like other biologics, can reduce exacerbation in the appropriate patient population, but more importantly, it also gives me reassurance that also, not only exacerbations, which are important, but also I can see lung function change. That lung function change is not as dramatic of what you see with bronchodilators, for example, but still it reassures me that the drug is working, doing something. And thirdly, it may also help me in predicting who may have the best response in lung function, such as the blood eosinophils, the severity of airway obstruction and the bronchodilator reversibility. These are the 3 parameters that we found.

Dr. Caudle:

Right, wonderful. Well, Dr. Hanania, thank you so much for joining me to discuss this new research with our ReachMD audience.

Dr. Hanania:
My pleasure. Thank you for inviting me.

Dr. Caudle:
For our last conversation here at the CHEST meeting, I'm joined by Dr. Eugene Bleecker, Professor of Medicine and Co-Chief of the Division of Genomics and Precision Medicine at the University of Arizona College of Medicine.

So, Dr. Bleecker, it's a pleasure to speak with you today.

Dr. Bleecker:
Pleasure to speak with you, Jennifer.

Dr. Caudle:
So you participated in 2 presentations here at the CHEST meeting, both of which focused on new data on benralizumab. So, why don't you tell us a bit more about that? Benralizumab was approved for asthma just last year, wasn't it?

Dr. Bleecker:
Yes, it was approved last year, and the 2 studies that I presented at the CHEST meetings were derivatives of the larger registration studies for benralizumab that were published last year in Lancet. Benralizumab is an anti-IL-5 receptor molecule. It differs a bit from the other anti-IL-5s, which are monoclonal antibodies toward IL-5. This actually binds to the receptor on eosinophils and some other active cells and causes a cytolytic process, so it really decreases eosinophils quite quickly, quite rapidly, and completely in patients seen in the 2 registration studies. The study itself, which these abstracts were derived from, showed that benralizumab in a bit over 2,000 people caused somewhere between a 30% and 50%, depending on the analysis, reduction in asthma exacerbations.

There were 2 different approaches toward drug delivery in these studies. One of them was a more traditional every 4 weeks, and one of them patients were loaded with the drug for 3 months every 4 weeks and then treated every 8 weeks and given placebo at the 4-week interval. And it turns out that the longer intervals were just as active as the shorter intervals, so this drug has been registered as an every-2-month drug, which is quite important because it allows patients to come into a healthcare facility at about an appropriate time to follow severe asthma.

As I said, it caused somewhere in the 30% to 50% range, depending on the analysis, of reduction in asthma exacerbations. This is over placebo. And it also produced a pretty significant improvement in lung function, average 150 mL above the placebo response, and finally, improved asthma quality of life. So it is very promising as another new targeted biologic to treat more severe asthma.

And by the way, the studies that I mentioned where I gave a range of response, they were due to the fact, in 1 of the 2 registration trials, CALIMA, more mild patients were admitted so they had fewer exacerbations and probably contributed less to that endpoint.

Dr. Caudle:
Understood. Well, it's really interesting. Your first talk today focused on an analysis of data from the SIROCCO and the CALIMA trials.

Dr. Bleeker:
The abstract that I presented today looked at how many patients within the SIROCCO and CALIMA trial who had greater than 300 blood eosinophils became exacerbation-free. And remember, everyone who entered the trial had to have at least 2 exacerbations in the past year. When we looked at that, we found that about 63%, 64% of the patients became exacerbation-free, and the numbers who had more than 2 exacerbations were reduced to about 16% or 17% of the population. So what you've done is shifted over the characteristics to having much fewer exacerbations. We also found that there was a slightly decreased number of a rare event, hospitalizations or emergency department visits. And very interestingly, the number of days patients had during an exacerbation was reduced by almost in half. In the placebo group, it was close to 12, and in the 2 active drug groups, it was 6. So, even if you had an exacerbation, it was shorter.

So I think this information provides important information on responsiveness to this agent, and it does show that we do have to learn more about how to really select the most responsive individuals and, perhaps, not treat individuals who may be less responsive.

Dr. Caudle:
You know, that's really helpful, and you've talked a lot about the analysis and the things that you've been looking at and what's been found, but what are some of the implications for clinical practice then? Can you take that 1 step further for us?

Dr. Bleecker:
Well, there are a lot of implications about these kinds of approaches for clinical practice. One of them is that the IL-5 drugs as a whole

seem to work on individuals with levels of eosinophils that are, perhaps, well within the normal limits. And what does that tell us? These are patients who were treated or exposed to either inhaled or systemic corticosteroids, and yet, they have some persistence of eosinophils primarily in their blood and in some studies in measures of airway eosinophilia, so that means they are probably somewhat less responsive, a characteristic of severe asthma to corticosteroid therapy. So we're beginning to say that these kinds of targeted therapies will improve individuals with severe asthma, and we really need to select who they are. And because these eosinophil numbers that we've talked about are relatively lower, it gives you other parameters to predict response, and the types of things I would look for besides blood eosinophils, which is readily available, would be presence of nasal polyps, older onset of disease, more severe airflow obstruction, lower lung function on spirometry, and presence of higher frequency of exacerbations.

Dr. Caudle:
So we've been discussing the data from the SIROCCO and CALIMA trials. What else would you like to add about those trials?

Dr. Bleecker:
Sure. The second abstract was really less of a pooled analysis to examine therapeutic drug and phenotypic interactions but was really to understand some of the phenotypes in individuals with eosinophil levels higher than 300. And remember, I said this is eosinophil levels that are elevated higher than you would expect in severe asthma but in patients receiving corticosteroids, so somewhat less responsive to corticosteroid therapy. And what was seen here is that individuals with higher blood eosinophils, over the threshold of 300, had more sinusitis, more nasal polyps and more other evidence of atopy, so this goes along with the kind of atopic phenomenon that may be seen in patients with eosinophilia and high and severe asthma. On the other hand, there was little difference in patients who had low eosinophils and high eosinophils. In fact, the low eosinophils were always slightly higher when we looked at a whole group of comorbidities that were less pulmonary or allergic, including obesity, diabetes, metabolic diseases and other things. So within that context, it may mean that noneosinophilic or T2 asthma may have more of these comorbidities, or some of them, such as obesity, may actually be related to one of our therapies, exposure to corticosteroids.

Dr. Caudle:
Okay, great. And what about this can we take away and apply to our clinical practice?

Dr. Bleecker:
Well, I think the whole thought in this whole aspect of subanalyses of the data is to better understand with a relatively expensive biologic who benefits the most, and you really have to take these abstracts in the context of the 2 subanalyses papers that I talked to you about, and that we're beginning to paint a picture that it isn't just individuals with higher eosinophils who respond to this particular anti-IL-5 but a cadre of other things. And I mentioned them before: nasal polyps, sinusitis, some aspects of the disease, low lung function, potentially hyperinflation, older onset—and that's very interesting because you'd expect, perhaps, earlier onset to respond better, but older onset appears to—very much more severe disease, meaning steroid-dependent, and frequency of exacerbations. And this picture will help you clinically to say, "Who should I choose this class of drugs to treat versus another class of drugs?"

Dr. Caudle:
Understood. And finally, what would you say are the most important takeaway messages from your talks at the CHEST meeting?

Dr. Bleecker:
Oh, the most important takeaway messages from my talks are that in a majority of individuals, therapy with an anti-IL-5 causes them to have no asthma exacerbations during the treatment phase of this study. There is a subset who continues to exacerbate, and we need to learn more about that smaller subset. As I said, it was about 15% to 16% who had more than 1 exacerbation. And in that subset, we have to learn whether maybe other therapies might be effective or whether other treatments, including looking at adherence and looking for other comorbidities, might be important.

Dr. Caudle:
Excellent. Dr. Bleecker, thank you so much for joining us today to discuss your presentations and the new data on benralizumab.

Dr. Bleecker:
Thank you.

Dr. Caudle:
I would like to thank all of our guests for helping us better understand the emerging science of severe asthma, the new approaches to its treatment and what the future might hold for clinicians and their patients. This is CME on ReachMD, and I'm Dr. Jennifer Caudle. Thank you for joining us.

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