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https://reachmd.com/programs/cme/advances-in-severe-asthma-highlights-from-chest-2019/11072/

Released: 11/13/2019
Valid until: 11/12/2020
Time needed to complete: 15 Minutes

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Advances in Severe Asthma: Highlights from CHEST 2019

Announcer:
Welcome to CME on ReachMD. The following activity, Advances in Severe Asthma: Highlights from CHEST 2019, is provided in partnership with Prova Education and is supported by an educational grant from Regeneron Pharmaceuticals.

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Your faculty are Dr. Nicola A. Hanania, and Dr. Reynold A. Panettieri, Jr.

Dr. Hanania:
Nearly half of patients with asthma have poorly controlled disease despite the availability of guidelines-recommended step-wise treatment approach that emphasize continuous assessment and readjustment of treatment. This comes in part due to suboptimal guideline implementation, over-reliance on short-acting beta agonists, and underutilization of maintenance therapy. Recent advances in our understanding of the pathophysiology of asthma have led to improved control, particularly for those patients with moderate to severe disease who remain uncontrolled on current traditional asthma therapies.

This is CME on Reach MD, and I'm Dr. Nic Hanania, Director of Airway Clinical Research Center at Baylor College of Medicine in Houston, Texas. And with me is Dr. Rey Panettieri Rey, welcome to the program. So, to start off Rey, why is it that we continue to see uncontrolled asthma patients despite adequate therapy and optimization of the management? And how is the information here from CHEST meeting help us in understanding this and maybe help our patients?

Dr. Panettieri:
Nic, great to see you, and thanks. You know the CHEST meeting here in New Orleans has been fascinating. It's really giving us a lot of insight into some of the obstacles that we, as clinicians, face in managing patients with severe uncontrolled asthma.

And I think for those listening, what's the big take-away? The big take-away is consider the pathogenesis of asthma or the phenotype endotype is T2 high versus T2 low. And that is going to be characterized exclusively for the use of biomarkers. That is, the serum eosinophil count, the total IgE – the specific IgE, and in some instances FENO; that is the fractional expired nitric oxide levels. These three – these three incredibly important biomarkers will characterize a patient as T2 high versus T2 low. That has implications for the management of the disease.
So let me transition to a question that I know is near and dear to your heart. It's very relevant in the LIBERTY – the LIBERTY study, one of the registration studies and the post hoc analysis. One extra thing really caught my eye was the fact that the age of onset or the duration of the asthma didn't really suggest responder/non-responder to dupilumab, right? That is the anti-IL4 receptor alpha antagonist or antibody; that it worked across all duration of disease and onset of the disease. Can you tell us a little bit more details, Nic, on that study? I know it probably caught your eye too.

Dr. Hanania:
Yes. And I actually presented the data this morning on this particular topic. In fact, when we looked at the QUEST data, which included 1,900 patients with moderate-severe asthma, we actually looked at patient's age of onset. Obviously, this is self-reported, so we look at patients who had asthma before age 40, or had asthma at age 40 or above. And particularly, we were interested, whether the response

to dupilumab – these are all patients with moderate-severe asthma, we wanted to see if their response is different. And indeed there was a slight difference where we saw a better effect on exacerbation reduction with dupilumab if they had late-onset asthma, but the lung function improvement was very consistent in both groups. Now, that tends to bring up the question: Why is it that late-onset asthmatics have a slightly higher response on exacerbation with dupilumab, whether they're original therapy, they're not using the inhaler correctly, whether they have more severe disease, and that's where there's more room for improvement. That remains to be answered.

Yeah, I was interested, Rey, in one of the sessions you were part of, at least as a presenter, on personalization of therapy in asthma. We were just talking about, you know, how it's important to personalize. And I'm just wondering what your thoughts about it? And if you can tell us something about that, that would be very helpful.

Dr. Panettieri:
Yeah, thanks, Nic. That session was an exciting session. I presented along with three other colleagues who really addressed a fascinating question: How do we characterize adherence? How do we examine patient-reported outcomes more definitively? And what I presented was the architecture or the signature of the provider and the patient alignment with improved outcome. So let me start with what we showed. This was a study in CHRONICLE, where we asked the interesting question: How well do providers predict control as compared to patients? Now, this has been studied in other venues, but what was intriguing here is we used the ACT test to characterize the patient-reported outcomes, and to correlate that with the physician's notion of control. And what we found is when the patient was asked: Is your asthma controlled; yes/no? They 75-80% of the time was very accurate in the control of their disease as demonstrated by the ACT test. Now, take that same group and ask the providers: Is this patient controlled; yes/no? It was a coin toss when you compared the provider's notion of control to the ACT test. In other words, the provider could not accurately determine what the ACT test was going to tell us about the patient's control. Yet if the patient said they were uncontrolled, the ACT test concordance was spot on. That's fascinating. That really suggests to us as providers, asking a patient how they're doing may be helpful in characterizing their disease, but our own preconceived notion of control was inadequate. So what's the take-away from that? The take-away is really we need to do objective measures of validated questionnaires like ACT to determine whether the patient is controlled or uncontrolled. Or maybe, Nic, what we do is simply ask the patient: Are you controlled? And the preconceived notion that we have in our own head takes the back seat. Now, one of our other colleagues looked at the digital readout of rescue inhaler, and what we found, and maybe not surprising, is the digital readout, the imprinting of that, really suggests patients are using the rescue inhaler far more often than the provider predicts or that even the patient reports face to face. So these were some of the real topics. I think we're learning about pragmatic real-life studies. How do we characterize adherence? How do we characterize disease severity? How do we characterize what the patient really is doing versus our preconceived notions? These are some of the challenges that we face, but hopefully will improve in the future.

So, Nic, you presented several abstracts at the conference. One of them on reducing severe exacerbations in corticosteroid-dependent severe asthma. Another look at omalizumab in patients with fixed airflow obstruction. Can you give us some of those highlights? I found the abstract fascinating.

Dr. Hanania:
Yeah. Yes, thanks, Rey. So the first abstract was analysis of data from the large VENTURE study, which as you know, Rey, was published last year, and it looked at patients with severe asthma who are oral steroid-dependent. And the question was in the main study to see whether dupilumab, an anti-IL4 receptor, can actually allow us to reduce or stop oral steroids in these severe asthmatics. And the main study shows that it can, compared to placebo, it can reduce the dose or even amount of oral steroids the patient needs, but at the same time can improve lung function and reduce exacerbation. So there are really three advantages. So in this subanalysis of VENTURE, we really posed the question of was there lung function improvement at 12 weeks? And we defined it as other improvement by 100 mL or 200 mL at 12 weeks, can actually reflect other improvement or not improvement make a difference in the exacerbation reduction at the end of the study, which is at 24 weeks or a six-month study. And the answer is simply, it doesn't. So there's really no – even though there was a trend that patients with higher lung function improvement had probably a better effect on exacerbation reduction, but we saw also reduction exacerbation in those who did not have big lung function improvement. And then the second abstract we presented was on a study that we were involved in many years ago, involving omalizumab, an anti-IgE called the EXTRA study. And we were interested to see also regarding lung function improvement, but here we looked at baseline characteristics of the patient, and we wanted to see if somebody with fixed airway obstruction at baseline, we defined it as an FEV1 less than 0.7, whether patients with low bronchodilator reversibility, meaning improvement less than 12% at baseline to albuterol. So both of these subgroups we looked at, whether that can reflect change in exacerbation or a change in the lung function over the one year of the study. The bottom line, what we found, is that bronchodilator reversibility 12% or more was an important determinate of reduction in exacerbation, meaning patients who have more than 12% reversibility at baseline had actually more pronounced reduction in exacerbation, whether they had fixed airway obstruction or not. When we looked at lung function improvement, there was a difference. Those – the only

patients who had good lung function improvement, which was significant, were those with bronchodilator reversibility, meaning the ones who have more than 12% and no fixed airway obstruction were the ones who had the best lung function improvement in the one-year study. Where we concluded that those patients with fixed airway obstruction and no reversibility may actually constitute a different phenotype in asthma. Particularly with omalizumab, I think the notion that it may not improve lung function in general is not correct because there are some subgroups of these patients can indeed have lung function improvement. We are just trying to define which of these subgroups. In this analysis, we found that bronchodilator reversibility at baseline is a good determinate.

Dr. Panettieri:
So those are really interesting studies. That first study that you talk about with dupilumab is very important because we like to almost use a bail fast phenomenon when we use biologics. We have choices now. But what I'm hearing clearly is that change in the FEV1 early in the institution of a drug like dupilumab may not tell the complete tale with regard to exacerbation and, by extension, even in OCS burden relief. That's a very important point. So how does the practitioner, the provider, utilize that data? Well, you don't get a big change, or if you do get a big change, there could be better benefits or the determination of a responder takes a little bit more time than us quickly looking at the big change in an FEV1 early. Now, the other point you mentioned was those patients who had twitchy airways, or more twitchy airways in the case of the omalizumab, may have a different outcome long-term with regards to exacerbations. In both of these points, in both of these studies, the metric of success is exacerbation, because exacerbations lead to greater OCS burden, and the consequences for adverse effects of our therapy. So I think these points are really elucidating, Nic. Great job. These abstracts are going to maybe change behavior of the provider in the prediction of response.

Dr. Hanania:
That was the whole purpose of this. You know, we had a session also at CHEST on biomarkers and where we are with biomarkers. I know you're interested in this area, Rey. And in one of the sessions I spoke at, we discussed both sputum and blood biomarkers, but also exhaled biomarkers. And another speaker talked about airway hyperresponsiveness as a potential biomarker, more so for diagnostic purposes. And so for example, I talked about whether blood eosinophils can be good predictors of response, but also good prognostic biomarkers, and certainly they may identify patients at high risk of exacerbation. I also talked about some of the biomarkers in the pipeline in blood that are still being looked at; certainly some of these are eosinophilic proteins. And also talked about sputum, although many centers don't do sputum induction, but certainly the sputum biomarkers may be better, although not as practical as blood biomarkers. So, Rey, this has been really a very valuable discussion. And I thank you for your time. And before we wrap up, Rey, do you have any take-home message for our audience.

Dr. Panettieri:
Yeah, Nic, this was a pleasure. Wonderful chatting about the hot items at CHEST 2019. So what are my key take-aways? My key take-away is stay tuned, there's going to be a lot more you're going to hear. This is a new world with regard to the management of severe asthma. We never had biologics this effective. The whole concept of precision medicine is thrilling and it's come to a station near you. We now have these tools. I feel that we're even better off than the rheumatologists using anti-TNF drugs in RA. We're talking about precise therapies for severe asthma. Key take-away; got to measure biomarkers. Without biomarkers, you're not going to know if a patient is high T2, low T2, or the specific category of T2; be it mast cell basophil-driven disease, versus eosinophilic-driven disease versus epithelial-mediated inflammation. There's overlap, but this is a great time to really discriminate the right patient for the right drug at the right time. Nic, what are your key take-aways at CHEST 2019?

Dr. Hanania:
Well, I'm really excited about asthma. Of course, we know it's a very old disease, but the new look at asthma is exciting because I think we have some more to offer to our patients with severe disease. Of course, I did take away like some of the things you talked about, trying to identify the subtypes of asthma, the predictors of response, involving the patients in decision-making, but also more personalizing the approach to treatment and really believing that this is not a one-size-fits-all disease; our very important take-away from this meeting. But also another take-away is that we are not there yet. We have other things to do, and we need to look more and more for interventions, but also looking at outcomes. As you said, we're getting there. Precision medicine for asthma is something that we really need to work hard on and hopefully we'll get there sometime. With that, I'd like to thank you again, Rey, for this nice conversation. And I wish you a very good day.

Dr. Panettieri:
Nic, I really appreciate this wonderful opportunity. It's always a pleasure chatting about asthma.

Announcer:
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