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Advances in Severe Asthma: Highlights from ACAAI 2019

Announcer:

Welcome to CME on ReachMD. The following activity, Advances in Severe Asthma: Highlights from ACAAI 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. Panettieri:

Despite the availability of guidelines-recommended, step-wise treatment approaches, nearly half of all patients with asthma have poorly controlled or uncontrolled disease. Now, in large part this is due to suboptimal guideline implementation, a lack of understanding of the pathophysiology of the type 2 inflammatory process underlying this disease and initiating patients on targeted therapies that can address this process. Now, recent advances in our understanding of the type 2 inflammatory process has led to improved control, particularly—now particularly for those patients with moderate to severe asthma who remain uncontrolled on current traditional therapies.

This is CME on ReachMD, and I'm Dr. Reynold A. Panettieri, Jr. Joining me to discuss these advances and data presented at the 2019 American College of Allergy, Asthma and Immunology Annual Meeting in Houston is Dr. Nic Hanania. Nic, welcome.

Dr. Hanania:

Thank you very much, Ray. It's good to talk to you.

Dr. Panettieri:

So the meeting was really exciting. Let's punctuate what we've learned in the next discussion. So, to start us off, Nic, many of us are probably well familiar with Asthma Impairment and Risk Questionnaire, or the AIRQ, and Air Compass, tools used to identify patients with higher-risk or uncontrolled asthma and to aid in shared decision-making. Shared decision-making is so important today when we have options. What we don't always know is the accuracy and the utility tool. Well, there's one abstract that assessed the tools. What did you think about it, Nic?

Dr. Hanania:

Well, I agree with you, Ray. We have several questionnaires to assess asthma control in clinical practice. The AIR-Q was a bit interesting because it targeted patients with uncontrolled disease, and it is a 10-item questionnaire that is self-administered. And it really looks at the risks and impairment and risk of these patients with uncontrolled disease. And in this particular poster that was presented at the college meeting, investigators looked at the utility and the patient's preference in using this type of questionnaire. This was tested in six sites; two allergy, two pulmonary, and two primary care sites. And the bottom line is, from the patient's perspective, when they looked at their preference, this type of questionnaire is something the patient preferred, and they thought that this questionnaire got them more communication with their physician about their disease. So I'm hoping that, in this type of questionnaire will be utilized more frequently, particularly in our practices where we see more severe patients and uncontrolled patients with asthma.

Dr. Panettieri:

Truly, Nic, this was exciting. I had one follow-up question though. Many of us use the Asthma Control Test. Do you see the AIRQ as having a different niche? Is it going to fulfill another need where many will go to AIRQ over the ACT?

Dr. Hanania:

Well, Ray, this is an interesting question. I think the ACT is still important because, first of all, it's a short-term questionnaire, it's a 5-item questionnaire. And it actually tests whether the patient is uncontrolled, well controlled, or very poorly controlled, or the patient is controlled. So I think it's a quick way to basically use in all patients with asthma. The AIR-Q was a bit more specific for uncontrolled disease in more severe patients, so particularly it may – the utility of it may be more in the asthma specialist's corner rather than in the general practice. So I think while there are no head-to-head comparisons between these two questionnaires, both may have utility where one being for the whole general asthma population, and the other one is more specific for more severe patients or uncontrolled disease patients.

So Ray, let me ask you. There were several posters and abstracts regarding the burden of oral steroids that touch base on that particular subject. As we know, it's a major issue in managing severe asthma. And can you maybe summarize some of these posters that looked at this? I would recall maybe three or four presentation focused on that particular topic.

Dr. Panettieri:

You're right, Nic. There was a cluster of abstracts around OCS burden; that is oral corticosteroid burden. I like to call out 2 of these: Patterns of Systemic Corticosteroid Exposure for Patients with Persistent Asthma, a US Administrative Claims study, and another that really focused specifically on pediatrics, among children and adolescents, and that was Adverse Events Associated with Systemic Corticosteroid Use Among Children and Adolescents with Asthma. Now, both of these posters were well... The studies were well designed. They were administrative database analyses. The first one I mentioned was from Kaiser Permanente, and pretty resoundingly the data shows that we are using way too much oral corticosteroids. It's the go-to drug for exacerbations, but when patients are having 2 to 3 exacerbations or 2 to 3 tapers a year, if you look at the OCS burden that's attendant with that, it's substantial. And the first paper and the first work really focused on the adult patient use, and again, we're using way too much oral corticosteroids, and the cost of that is astounding. You're seeing a fair amount of cost mostly due to second adverse effects and systemic consequences.

Now, in the second poster, the focus was really on children, and this was work looking at a large database, and again, what we find is that children or adolescents that were put on OCS and not maintenance—we're talking about frequent exacerbators—really experienced numerous adverse effects.

Now, the bottom line here is many times patient gets put on oral steroids not only by the primary care physician but by the specialist or by yet another provider. Often the provider is unaware that the patient is also receiving high-dose steroids or tapers by other providers. Drilling down to the administrative databases, we're learning more about how truly prevalent our use, or I would say abuse, of oral corticosteroids are.

Dr. Hanania:

That is very interesting, Ray. I think, you know, now that we have options to reduce the burden of oral steroids in patients with uncontrolled and severe disease, we should really try to capitalize on those options. I think those abstracts show really a couple of things; one is we utilize oral steroids more than what we think we do. And even short courses have tremendous burden on the patients. And so I think one has to be cognitive of this, especially if there are other options for managing these patients.

Dr. Panettieri:

For the next series of posters from the College meeting, Dr. Hanania, let's talk about the progress we've made with biologic therapies. You just mentioned the alternative to OCS is really biologics, right? There were some very interesting abstracts here. Why don't you help us walk through the couple that really impressed you on the focus of biologics in uncontrolled and severe asthma?

Dr. Hanania:

Sure, Ray, there were indeed several posters and presentations on biologics and severe asthma, and it's amazing how this area of science is growing fast. One of the posters that I was involved in, and actually it's a study looking at claims database from the United States, and we really wanted to know what sort of patients are usually started on biologics. And so we tagged on a large database that included more than 23 million patient's data. And we identified patients who were started initially on biologics but were not on it three years before that. And we wanted to know what are the immediate reasons for them to be started on biologics. And obviously, not to our surprise, that many of these patients had significant healthcare utilization or needed oral steroids; 56% of them had oral steroids at least once in the last two years before being prescribed a biologic. And 26% had emergency room visits. So I think we are utilizing biologics in the right way, in the right population basically. That study at least suggests that these patients are sick and, despite everything they're on, they needed something else. However, there were several abstracts that looked at some analysis of larger clinical trials that have already been published. Some of these abstracts looked at the anti IL-4 receptor, dupilumab and, particularly one of them looked at

whether IgE level percent at baseline predicts response to dupilumab in patients with uncontrolled severe asthma. And they looked at exacerbation. This was a part of a large study, and they mainly looked at the symptom control, as well, from the QUEST study, which included a large number of patients with uncontrolled disease. And that showed dupilumab as efficacious in reducing exacerbation. But here in this analysis, they were interested in looking at asthma control in patients with different levels of baseline IgE, immunoglobulin-E, and looked at patients with less than 100, 100-250, and more than 500. And the reason why because IL4 is an important as you know for IgE production, so they wanted to know if the efficacy of this drug is more in one group versus the other. The bottom line is symptom control of asthma was very similar in all these three groups of patients, no matter what their IgE level was at baseline. And another interesting slide presentation on a study looking at also dupilumab in this large QUEST study, but particularly looking at those patients who were sensitized to fungus, mainly aspergillus. And so, as you know, ABPA, allergic bronchopulmonary aspiration, is a very important problem in subgroup of patients with asthma who tend to be oral steroid-dependent and very hard to treat. And indeed in the QUEST study, there were patients who were sensitized to aspergillus and had high IgE and high, and basically have ABPA. And in this analysis, although the group is small, they compared that with a larger group of patients in the study. And the bottom line, these patients had similar response to dupilumab with reduction in exacerbation and improvement in lung function with dupilumab versus placebo over the course of this study, which is very reassuring, even in those sick patients who have sensitization to aspergillus, this drug would work.

Well, shifting gears towards other studies on biomarkers, one study looked at, although a very small study, looked at the effect of dupilumab on exhaled nitric oxide levels, which is a very important biomarker to predict response to dupilumab, but also here they showed that a FeNO exhaled nitric oxide actually is a very good pharmacodynamic biomarker where the levels of FeNO go down with treatment, which is something that can help clinicians once they're starting this drug. There were a couple of abstracts looking at other biologics targeting interleukin-5. As we know, interleukin-5, there are three drugs in the U.S. The study that I'm quoting actually was a sub-analysis of a large – two large studies looking at the benralizumab, which is an anti-IL5 receptor, and particularly looking at those patients with nasal polyps. We know from previous studies, that the presence of nasal polyps may be a good predictor of response to an anti-IL5 agent. And here, benralizumab was the drug that they looked at. And they were more interested to see if – whether the patient had nasal polyps removed or not removed, meaning having had surgery or not. They also looked at whether the subgroup of patients had aspirin sensitization or not, and whether their response to benralizumab was different. At the bottom line, they also looked at IgE level in this analysis, as well. And all these subgroups of patients had a good response in reduction exacerbation and improvement in symptoms, whether they had polypectomy in the past or not, or whether they had aspirin sensitization or not. So certainly giving us reassurance that these patients would respond to this anti-IL5 receptor. So as you know, you see we have – there were other studies also, but these are the main ones I was interested in. But you know, we have come quite a bit of forward in advancing our knowledge, and knowledge about biologics and their use, to the extent that now we're looking at subpopulations to see if they're responding better or less, which is very reassuring to see these data accumulate over the time being.

Dr. Panettieri:

Truly, these abstracts have expanded our knowledge and extended our knowledge into what is the right patient for the right drug at the right time. I'm really encouraged about this, and I think it will lead into our next discussion on real-life, pragmatic studies, but I think what you've just highlighted is the more we can identify, predict therapeutic response given comorbidities with biologics, far better will we be in helping patients with a specific therapy.

Dr. Hanania:

Yes, indeed, Ray. In fact, now that we have these biologics approved, and some of them for a long time, and others for a shorter period of time, we are able to look at them in the real-world scenario. In fact, I was interesting – interested to see that, at the college meeting, there were several presentations on real-world studies with these biologics, and that gives us reassurance that they work, that they are safe. Maybe if you don't mind giving us your take on some of these studies presented on the real-world use of these biologics in the large populations.

Dr. Panettieri:

So, Nic, it's interesting that when registration studies for a drug are put in the hands of the FDA, often the patients that get such therapies are not really aligned with the way we typically will use these medicines in real life, so real-life, pragmatic studies are incredibly important in understanding who really benefits from these therapies. As you mentioned, there were several—actually 4 posters I'd like to call out here that address pragmatic, real-life studies. The first 2 were extensions of the PROSPERO study. Now, this focused on omalizumab and asking really very, very focused questions on what about the numbers of specific allergens that a patient is sensitive to. Are they predictors of a response to omalizumab? Now, we know total IgE is not really a great predictor, but in this paper they addressed what about specific IgE from those with 1 or 2 up to maybe even 4, and surprisingly, those patients who were placed on the omalizumab had equal benefit, equal benefit from omalizumab across the numbers of specific IgEs that were recognized, so that's quite

intriguing. This drug works whether you are sensitive to 1 or to 5, and maybe a priori we would have thought those with more specific IgE sensitivities would have been the better responders, but the drug appears to work across that atopic group once you've defined it by a specific IgE sensitivity.

The second study really looked at reversibility, and the question here was: What about responsiveness to omalizumab if you're high or low airway reversibility? Now, remember, in the IL-5 registration studies, the anti-IL-5 registration studies, all of those studies got enrolled with patients with significant pre and post bronchodilator response. In the study that was done, the PROSPERO study, looking at real-life, pragmatic studies, curiously, omalizumab would work whether you had high or low reversibility, and indeed, exacerbation rates were diminished in both of those groups.

Another study which focused on mepolizumab in real-life studies was interesting, and it showed that with exacerbation reduction, there was an associated decreased cost, and that cost was almost 40, approaching 50% decrease when patients were put on mepolizumab and one costed out what an exacerbation truly was.

And the last study, this was a reslizumab study that was really focused on improved patient outcomes. This is a study that I had coauthored with Mike Wechsler from National Jewish. What we found is in this real-life, pragmatic study, that indeed, patients who were placed on reslizumab—remember, this is pragmatic and real-life, not placebo-controlled—clearly had decreased exacerbations and actually decreased oral corticosteroid burden. Previous to this, reslizumab had not done a true OCS burden comparing, but the real-life data, at least as we reported, seemingly demonstrates that reslizumab, using a BMI or weight-based dosing scheme, decreased OCS burden and exacerbations. So all told, really exciting pragmatic data giving us a sense of what providers are using and how these drugs can actually benefit patients.

Dr. Hanania:

Well, thank you very much, Ray, for this wonderful summary on your insight in the real-world studies. Indeed, I think real-world studies are important to reassure us as clinicians about the effectiveness of these agents, but also their long-term safety, even in subpopulations that were not studied in the clinical trials. I think the longer we use these drugs, the more acquainted we become and the more reassuring about their safety and effectiveness, I think these are – the ones that you mentioned are only a few of several other real-world studies being done, which are very important for us treating these patients with severe asthma.

Oh, Ray, thank you very much for having me. I think in this short period of time, I hope we were able to summarize some of the important developments in this field, and are sort of continuously learning. And it's a pleasure to join you to discuss these.

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