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The Role of Targeted Therapy in Severe Asthma with Type 2 Inflammation

Announcer:
Welcome to CME on ReachMD. This activity, titled "The Role of Targeted Therapy in Severe Asthma with Type 2 Inflammation,"is brought to you by CHEST. This educational activity is supported by an educational grant from GlaxoSmithKline and an educational grant from Genentech, a member of the Roche Group.

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Here's your host, Dr. Sandra Adams, a Professor of Medicine in the Pulmonary and Critical Care Division of UT Health San Antonio and Staff Physician at the South Texas Veterans Health Care System.

Dr. Adams:
Therapy for severe asthma has been revolutionized over the last few years by the availability of targeted therapy for type 2 inflammation. This is why, today, we will be discussing how to incorporate readily available biomarkers to identify different phenotypes of asthma in order to target therapy and how to best assess response.

This is CME on ReachMD, and I'm Dr. Sandra Adams. Here with me today is Dr. Mario Castro, Chief of Pulmonary, Critical Care, and Sleep Medicine at the University of Kansas School of Medicine.

Dr. Castro, welcome to the program.

Dr. Castro:
Thank you, Dr. Adams.

Dr. Adams:
To start off, Dr. Castro, can you walk us through the targeted therapies that are available for severe asthma with type 2 inflammation?

Dr. Castro:
Sure. The 5 biologics that are currently approved, one of them has been now around for 15 years. Omalizumab, it is a monoclonal antibody against IgE, and it's indicated for patients with severe, persistent allergic asthma, ages 6 and older. We now have 3 anti-IL-5 medications that are approved for the treatment of patients' severe persistent asthma in the US. This is reslizumab, mepolizumab and benralizumab. These 3 anti-IL-5 agents are pretty similar in terms of their efficacy for the treatment of severe, persistent asthma. The main difference is reslizumab is only available intravenously while mepolizumab and benralizumab are available subcutaneously. These products are available currently in the US for, again, treatment of severe asthma, whereas mepolizumab also has a second indication for the treatment of EGPA, or eosinophilic granulomatous polyangiitis, or what used to be called Churg-Strauss syndrome. The fifth biologic we have available in the US is dupilumab, and it has several indications. It was approved first for atopic dermatitis and then for moderate to severe asthma with an eosinophilic phenotype and then most recently for chronic rhinosinusitis with nasal polyposis. It's mechanism of action is inhibiting anti-IL-4 alpha receptor. By inhibiting that receptor, it's able to block the actions of both IL-4 and IL-13 to the 2 key Th2 cytokines.

Dr. Adams:
Okay, that's great information for everybody, just a nice review. Can you tell us some of the efficacy data available to support the use of these targeted therapies like the types you just talked about on patients with severe asthma?

Dr. Castro:
Sure, and I'll just briefly cover the impact that these agents have on a couple of the key endpoints that we have studied them for and for which they were approved, which is exacerbations due to asthma—usually these are exacerbations that require oral corticosteroids—and then also impact on lung function in these patients. Now, when we think about omalizumab, the best study for that is the EXTRA study by Nick Hanania, and in that study it showed that asthma exacerbations were reduced by about 25% in those patients that have severe allergic asthma that fall within the IgE dosing criteria of 30–700. Now, impact on lung function, though, with omalizumab is less consistent. In fact, most studies have not shown a significant impact of omalizumab on lung function, which is an important concept to think about when you are selecting patients and deciding, "Does this patient's baseline lung function need improvement or not?"

The 3 anti-IL-5s that we mentioned- The first is mepolizumab, and mepolizumab, in the DREAM study and in the subsequent MENSA study, showed about a 50% reduction in exacerbations. Now, when we look at lung function with mepolizumab, it's a little bit less impressive. It's about 100 mL improvement over placebo. The mepolizumab also had a study called SIRUS which looked at reducing oral steroids in patients that were chronic oral steroid requiring and showed about a 50% reduction in oral steroids.

Now reslizumab also, similarly, has about a 50% reduction in exacerbations and a little bit more improvement in lung function, on the range of 100–130 mL over placebo.

Then lastly, with benralizumab, which is again the third anti-IL-5 but inhibits through the IL-5 receptor—benralizumab in its studies, SIROCCO and CALIMA, showed about a 50% reduction in exacerbations. It also, importantly, improved lung function, about 100–160 mL over placebo. In the ZONDA study, benralizumab showed that it was able to reduce the oral steroid dose by about 75%. Importantly, about half the patients treated with benralizumab that were requiring oral steroids chronically were able to come off their medication, their oral steroid, altogether.

The last biologic is dupilumab. Again, it's the IL-4 alpha receptor blocker. And dupilumab showed, in the QUEST study, again about a 50% reduction in exacerbations but importantly a significant improvement in lung function on the order of at least around 140–150 mL, and this was sustained over a year-long period of time. Now, dupilumab also did an oral steroid-dependent study called VENTURE, and VENTURE showed, again very similar to the benralizumab, that there was about a 70% reduction in oral steroid dose, and about half the patients were able to come off their oral steroids altogether. So these are some of the key results that we've seen with these 5 biologics and impacting, really, and a game-changer for our patients.

Dr. Adams:
It sounds like it. And I know that a lot of the patients out there have different characteristics. I'm interested in hearing your strategy about phenotyping and selecting which of these therapies is best for which patients.

Dr. Castro:
Yeah, and that's a difficult question from the standpoint we wish we had better biomarkers. I wish we had diabetes measures like we do with the glycosylate hemoglobin, but we don't have that, and so what we currently use are really 3 biomarkers in our management of patients with severe asthma. First, we can look at eosinophils, and typically we use the CBC with differential to look at the absolute eosinophil count. There we are looking for an eosinophil level of at least 150 or greater, but certainly most consider eosinophilia being significant at 300 or greater. And we think that blood eosinophils correlate to what is happening in the airway that we can measure in research studies with sputum eosinophils.

The second biomarker that we use pretty often is FeNO, which stands for fractional expired nitric oxide level. This is a test that is readily available. It can be measured even in the outpatient setting where you breathe into the device for about 10 seconds. What it does is it measures oxidative nitrative stress in the airways and also reflects mechanisms of IL-13-related inflammation in the airway. FeNO then allows us to reflect the actual inflammation that is in the airway of these patients. We typically say a FeNO level of greater than 20 parts per billion reflects T2 inflammation.

The third biomarker we have is IgE, immunoglobulin E. And this has been around for a number of years, and we know it's a marker of allergic asthma, and we know that when it is elevated it certainly can indicate allergic disease, but then we have to order specific IgE depending on the region of the country of what are the dominant allergens in that region of the country to understand that patient's allergic asthma better. The one thing that is interesting about IgE, it does not predict response to anti-IgE therapy, whereas elevated EOS and elevated FeNO do predict response to biologic therapy with the greater the blood eosinophil count reflecting, in general, a better response to anti-IL-5 therapy.

Dr. Adams:
That's great information. So, for those of you just joining us, this is CME on ReachMD. I'm Dr. Sandra Adams, and today I'm joined by Dr. Mario Castro to discuss targeted therapy in patients with severe asthma with type 2 inflammation.

Dr. Castro, let's continue with me asking: How do you recommend monitoring a patient's response to therapy? In other words, what are the subjective and objective criteria you use? And then how soon do you follow-up your patients to assess their response to therapy?

Dr. Castro:
Thanks, Dr. Adams. I think this is an important question because we all struggle a little bit in terms of how to correctly follow our patients with a chronic disease, and asthma is certainly no different. What we found is that there are really 3 things that I can use to monitor my patient's response to therapy. The first I use is the Asthma Control Test. This is a symptomatic questionnaire that patients can fill out. I typically just have it on a clipboard in the office, and they fill it out while they are waiting for me, and then I review that with them. The Asthma Control Test is very helpful because it gives you an objective measurement of asthma control reported by the patient. For a response, we are wanting to see a shift of at least 3 or more in the Asthma Control Test score, the ACT.

Now, the second measure I use is lung function, and what we do with lung function is we measure spirometry. Most practices have access to a pulmonary function lab or have a spirometer in their practice. And what we are looking for is an improvement in the FEV1 of at least 100–150 mL from their prior baseline, so that indicates to us a lung function responder.

Then the last criteria that I use is exacerbations. We want to reduce exacerbations often with these biologic therapies, and typically what we are looking for is at least a 50% reduction in their exacerbations, ideally getting to 0, but we know that some patients are just going to encounter a viral infection and exacerbate, so you want to see at least a reduction of about 50% from their prior year's baseline.

The last thing I sometimes use in a subset of patients is those that require chronic oral steroids. In those patients I'm looking for at least a 50% reduction in their oral steroid dose. For example, if they were taking 20 mg a day of prednisone per day and I start a biologic, I want to see that patient actually go down to 10 mg or less—and ideally, of course, off altogether because of long-term steroid effects.

Now, how do we time this in terms of how long do we keep these therapies on? Certainly, this is evolving, but the latest guidelines from GINA and other international guidelines suggest that you should be evaluating your patient's response to therapy on a regular basis and making a decision by 4 to 6 months. Certainly, by 6 months you can make a decision in most patients whether or not they are responding. If the patient doesn't have a response in this time period, then it is time to move on to a different class of biologic therapy. I have seen patients with elevated eosinophil counts, they should respond to anti-IL-5 therapy, but they don't, and it's maybe because the elevated eosinophil count is actually reflecting more T2 inflammation, and then you switch them over to an IL-4 receptor blocker, and then they respond. So, certainly we know that we sometimes have to just adjust the therapy within a relatively short period of time, and because of the expense of these biologics, we don't want to keep them on forever just to do something. We need to really discontinue an agent if it's not helping them or move on to a different class.

Dr. Adams:
Sure, that sounds like it makes a lot of sense and is very practical information. It sounds like we need to be flexible enough to change but really not just continue forever on one particular medicine.

So, Dr. Castro, just to bring our discussion to a close, what is at least 1 unmet need, and what are the future directions of targeted therapy in patients with severe asthma with type 2 inflammation that you would like to pass along to our listeners?

Dr. Castro:
Well, we really would like to have something that is not necessarily injectable. We would like to have something that you could either inhale, because a lot of our patients are very used to using inhaled therapy, or we would like to, of course, think of something that is oral. And certainly we know compliance would likely be very good with these routes of administration and allow us to kind of make it even broader available for our patients in terms of their access to this medication. So, certainly this is an unmet need for patients with type 2 inflammation at this point, and our hope is in the near future we will have those available.

Dr. Adams:
That would be great. Well, with those thoughtful comments, we are going to close the program today. I want to thank my colleague, Dr. Mario Castro, for sharing insights on how to best evaluate and treat patients with severe asthma with type 2 inflammation.

Dr. Castro, it was great having you on the program.

Dr. Castro:
Thank you, Dr. Adams, for having me, and I hope this is helpful to our listening audience.

Announcer:
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