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Advances in the Management of Difficult-to-Treat Asthma

Announcer:
Welcome to CME on ReachMD. The following activity titled, New and Emerging Treatment Strategies for Patients with Asthma: A Care Team Forum is jointly provided by the Postgraduate Institute for Medicine and RMEI Medical Education, LLC. Prior to beginning, please be sure to review the faculty information and disclosure statements as well as the learning objectives.

Dr. Panettieri:
I'm joined today by my colleagues, Mike Wechsler and Jonathan Corren, and my patient Amanda Sparbeck. Amanda is a fantastic demonstration of control of asthma after methodically going through a process of working up the disease and characterizing the disease. So, with that, I'd like Amanda, who is my patient, to describe her story as she understands it.

Amanda:
My name is Amanda. I was diagnosed with asthma when I was 29 years old. Prior to that, I had been a healthy child. I was barely ever sick. I never missed school. I was in dental school when I got sick. We were treating patients in the clinic, and in the beginning, I thought I was just catching colds from my patients, and I finally saw a physician who diagnosed me with bronchitis. And after the bronchitis was successfully treated, I was still having shortness of breath and difficulty breathing, and at that point he diagnosed me with asthma.

Dr. Panettieri:
Thank you, Amanda. Now, let me give you a little bit of the back story of Amanda's workup, which was very important. Amanda was a lifelong nonsmoker. She was atopic, and she was allergic to several both perennial and seasonal allergens. Her FEV1, or spirometry, showed her to be about 85% predicted when healthy. However, with exacerbations or uncontrolled asthma, her FEV1 would drop to 62–65%. Now, in the workup we also discovered that she had quite the bronchodilator response. Her FEV1 improved by 15%. Further in her workup we identified that her exhaled NO was 32 parts per billion. This was at baseline, not in an exacerbation. And we also recognized that her peripheral eosinophil count was about 480, quite elevated. So, putting this all together, Amanda's picture was one of atopic, eosinophilic asthma, and at that point we had a variety of choices in her therapeutic management.

Dr. Wechsler, Mike, what do you think about Amanda? What do you think about the diagnosis and the characterization of her airway inflammation?

Dr. Wechsler:
Yeah, so Amanda presents a very interesting case of what I would probably call type 2 asthma. And when we think of asthma, you're right, Rey, that we now start to identify different types of asthma. Historically, we would just look at phenotypes, so the set of observable characteristics that an individual had which result from the interaction of the patients, the genotype of the patient and his or her environments, and so phenotype... There are several ways of looking at phenotype, but you can have trigger-induced asthma, so patients who have a history of allergies and they can tell you about their history of allergies. Patients can report exercise-induced asthma, occupational asthma. You can also get the patient characteristics and whether or not they have a smoking history, whether they are obese, whether they are elderly. And then you can look at their clinical presentation, whether they presented early in childhood or whether or not they presented later on in life, whether they are exacerbation prone or not, so those are the different phenotypes of asthma.

But we've moved beyond phenotypes to now talking about endotypes. An endotype is a relatively new term. It refers to the specific biologic mechanism that explains the observable characteristics of the individual, so it's the underlying mechanism. And so, broadly

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speaking, we have evolved from phenotypes to looking at the mechanisms and the endotypes, but the 2 can be related. When we talk about endotypes in asthma, we really think about 2 broad categories: type 2 asthma and non-type 2 asthma. Type 2 asthma is asthma that's brought forth by interleukin 4, interleukin 5 and interleukin 13, and it's characterized by the presence of eosinophils, nitric oxide and IgE levels, and so that's where Amanda's case really fits in, as opposed to non-type 2 asthma, which is not associated with any of those cytokines, not associated with any of those biomarkers, and is often associated with other factors like obesity or smoking or infections.

Dr. Panettieri:
So, in the beginning, Amanda, how was your asthma? Would you call it controlled? And then what happened over time? What were the major things that you realized characterized your asthma as poorly controlled?

Amanda:
Soon after my diagnosis I served in the military, and at that point I was just treating it with albuterol and prednisone. I was constantly taking prednisone and using the rescue inhaler, and the physicians there didn't seem to progress much in my treatment. We tried a few different allergy medications, but it didn't seem to help. And when I came home from the military and started working with Dr. Panettieri, we started trying other medications. I would have to nebulize in between treating my own patients because I was that short of breath. Walking to and from the car was difficult for me. Walking on the beach on vacations, I had to consider how quickly I would get winded. It was miserable, especially from... I was never very athletic, but I was always a healthy child. I mean, I didn't suffer with these kinds of things, so I can tell you that it was quite scary waking up in the middle of the night not being able to breathe. I had hospitalizations when I was in the military. It was scary, and I'm an adult, and it was so—a very scary experience for me.

Dr. Panettieri:
Now, Amanda, you also developed nasal polyps, and that required you to have surgery, correct?

Amanda:
That's correct. I actually had sinus surgery twice to remove polyps, and luckily, the last surgery was in 2009, yeah, and so I've been pretty lucky that they haven't recurred again, but, yeah, I mean, it was not fun.

Dr. Panettieri:
So, Jonathan, coming back around, let's talk about poorly controlled asthma within the context of the GINA guidelines. Tell us a little bit about that, especially as we transition to the use of biologics, Jonathan.

Dr. Corren:
A new version of the GINA guidelines came out in 2018 with more information added in 2019. What it intended to do was create a structure by which doctors to judge both the severity level of a patient's asthma as well as the level of control. And what was unique about the most recent GINA guidelines is it ascertains a patient's severity level by the amount of medication required to control their disease satisfactorily.

When we talk about moderate to severe asthma, we're talking about patients who require medium to high doses of inhaled corticosteroids with a second agent, usually a long-acting beta-adrenergic agonist taken by inhalation. In patients who are in this severity category requiring this amount of medication to control their disease, some will continue to have symptoms that are unmitigated, symptoms both during the day as well as night with nighttime awakening, inability to exercise, and other symptoms that get in the way of their daily life. Patients may also take a large amount or extra amount of inhaled beta agonists, short-acting beta agonists, in order to help control their symptoms. In some situations, despite all of this medication that the patient is taking on a regular basis, they will have exacerbations of their disease, and the GINA guideline tells us that either in the presence of symptoms, excessive beta agonist use and exacerbations that accrue 2 or more times per year, we can consider that patient to have poorly controlled asthma.

Dr. Panettieri:
Amanda, let me ask you about your initial therapy. This was prior to you and I really getting together to manage your disease. Tell me about the use of the compounds that you were on, like zafirlukast and montelukast, leukotriene modifiers. Were they effective? What were your inhalers like?

Amanda:
No, I mean, it was not effective. I basically went from flare-up to flare-up. There was never really any well-controlled period of time. We just didn't have success. And part of the difficulty may have been that physicians would change because I was in the military and so physicians would move to different duty stations and we were constantly starting over again, but I had zero success. Nothing really worked except for the prednisone, which isn't a great long-term solution.

Dr. Panettieri:

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Now, you did highlight the point that you got skin testing. You were positive. And then you transitioned to a biologic, and that was omalizumab. We have had that around for 16 years. In your case, was that a miracle drug?

Amanda:
No, it was not. In fact, I think I may have been on it perhaps a year, and there were no significant differences in my response. I mean, I was still having flare-ups that required prednisone, and I think that's when the decision was made to just discontinue it because it didn't have the effect on me that it did on a lot of other people who took it successfully.

Dr. Panettieri:
And you were taking it, right? I mean, you were getting direct-observed therapy, so this was not—

Amanda:
Yes, that was an injectable.

Dr. Panettieri:
Just wrong patient, wrong drug at the wrong time.

Amanda:
Right.

Dr. Panettieri:
So let's now transition. You've heard Amanda tell her story, the initial therapy, the initial failure. We've heard about endotypes. Mike, let's… Dr. Wechsler, let's get down into the weeds here. Tell us a little more about this high T2 low T2 inflammation. Can you give us a little more insight?

Dr. Wechsler:
Sure. So, what we've started to recognize is the different pathways that are involved in asthma pathophysiology, and we think of type 2 versus non-type 2 based on the cells that are involved and based on the mediators and based on the cytokines that are produced by many of those cells. So, for type 2 asthma, we think about the cytokines interleukin 4, interleukin 5 and interleukin 13, and we think about the cells that they have effects on. So, interleukin 4, 5 and 13 are made by Th2 cells, or T helper 2 cells. They are also made by innate lymphoid cells, or ILC2 cells, and hence, that's where the name type 2 comes from, from both Th2 and ILC2. IL-5 plays an important role in eosinophil production, eosinophil maturation, eosinophil proliferation and results in activation of eosinophils and production of all the eosinophilic mediators, things like major basic protein, eosinophil-derived neurotoxin, eosinophilic cationic protein, amongst others, and that causes eosinophilic inflammation, and that's one of the key cells that is involved in the pathophysiology of type 2 asthma.

But it's not the only cell. IL-4 is a cytokine that's also produced by T helper 2 cells, and that's involved in, first of all, B-cell production of IgE. And IgE is an antibody, as we know, that acts on mast cells in the context of the presence of allergens, and when 2 IgE antibodies on mast cells crosslink with an allergen, it causes the mast cell to degranulate and release its mediators, things like histamines and leukotrienes, so IL-4 plays an important role in IgE production. IL-4 also plays a role in eosinophil trafficking into the tissue.

Furthermore, the third cytokine that's involved in type 2 inflammation is IL-13, interleukin 13, and that's involved in mucous production, edema, and also nitric oxide production, so we've got 3 good biomarkers of type 2 inflammation. Things like eosinophils in the blood or in the sputum, nitric oxide, as well as IgE to some extent is a good biomarker that reflects type 2 inflammation.

In someone like Amanda, it's important to characterize what type of asthma she has, what are the cells that are involved, because she clearly has severe asthma. She's having frequent exacerbations, many symptoms, and we need to get her the right drug.

Dr. Panettieri:
Now we'll move on. So let's now take a look at currently approved biologics in the therapies and, again, consider Amanda within that context of the right drug for the right person at the right time. I'll talk about omalizumab. Omalizumab was approved in 2003, so 16 years we have had omalizumab, and this therapy, which targets the IgE molecule, binding the soluble IgE, preventing its binding to the FCS flawed receptor*14:38 has been demonstrated to clearly improve exacerbation rates and quality of life. In the case of Amanda, however, it was not that effective in her asthma.
Mike, do you want to talk about the anti-IL-5s and a little bit discrimination of the 3 drugs that are available?

Dr. Wechsler:
Yeah. We have 3 drugs that target either IL-5 or the IL-5 receptor. The first one that was approved was mepolizumab, which was approved in 2015. It's administered subcutaneously once a month. It was initially approved for in-office use, but in 2019, it became approved as well for at home use, and it's administered once a month with a dose of 100 mg subcutaneously. At that dose it's been

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shown to reduce asthma exacerbations by about 50% and to have significant impact on other asthma outcomes, including steroid reduction and including some modest improvements in symptoms and lung function amongst other things.

In 2016, the second anti-IL-5 therapy became approved, and that was reslizumab. Reslizumab is an intravenous preparation. It's administered 3 mg/kg on a monthly basis, and it too targets IL-5 and has been shown to reduce asthma exacerbations on the order of about 60% in patients who have eosinophil counts more than 400. It's dosed-based on body weight, so that's a certain advantage for heavier patients and in patients who may have higher eosinophil burden.

The third therapy that targets IL-5 is really benralizumab, which was approved in 2017, and it targets the alpha receptor of IL-5, so it targets the receptor upon which IL-5 binds, and by doing that it facilitates not just prevention of binding of IL-5, which can activate the eosinophils, but also, it can result in antibody-mediated, cell-dependent cytotoxicity and killing of the eosinophils, because the body may recognize the benralizumab on the receptor and identify it as a target that can end up being killed. What happens then is benralizumab ends up depleting eosinophil levels. So it's administered 30 mg subcutaneously once a month for 3 months, and then it can be administered every 8 weeks. That's a clear advantage there as well. It's been shown to reduce exacerbations anywhere from 30–50%. In patients who are given oral corticosteroids, there was a 70% reduction in asthma exacerbations with a concomitant 50% reduction in steroid dosing. So all these therapies are effective. They all tend to deplete eosinophils. There have been no head-to-head studies. And they are all quite effective for patients with eosinophilic asthma.
And the key is to identify patients who have eosinophilic asthma, either in the blood or in the sputum. The higher the eosinophil count, the more likely these patients are to have exacerbations, but also the more likely they are to respond to these therapies.

Dr. Panettieri:
Great, Mike. Jonathan, can you describe the first and only in its class anti-IL-4 receptor antagonist that's been approved for asthma? We're talking about dupilumab. Can you give us a little insight into its use in poorly controlled asthma?

Dr. Corren:
Rey, thank you for that very important question. In the past year, 2 pivotal trials were published with dupilumab, both in the New England Journal of Medicine, the first revolving around patients who had poorly controlled asthma despite using medium to high doses of inhaled corticosteroids plus inhaled long-acting beta agonists. That study included patients who both have non-type 2 or low type 2 as well as clearly demonstrated type 2 asthma. What was shown in that first trial was that patients who had eosinophil counts of 150 and up had significant reductions in asthma-related exacerbations. For patients who had eosinophil counts of 300 and up, there were reductions in asthma symptoms, improvements in quality of life and very large improvements in pulmonary function. The second trial dealt with patients who are the most severe to treat in our practices, and these are patients who are oral glucocorticoid-requiring patients who took doses anywhere from 5 mg up to 35 mg a day in order to control their disease. In that study patients were demonstrated to have a significant reduction in their oral corticosteroid requirement over a period of 6 months while at the same time demonstrating improvements both in pulmonary function and significant reductions in exacerbations. Together these 2 studies I think demonstrate the relevance and importance of IL4/13 blockade therapy in patients who have severe, uncontrolled asthma.

Dr. Panettieri:
So what I would like to do now is move on and ask my colleagues, Mike and Jonathan, to comment on the right patient, the right drug. We just heard and had a very nice review of all the biologics. There are going to be some specifically within an age category that are appropriate and approved and others that aren't. Mike, could you comment maybe on the IL-5s? And, Jonathan, if you could talk about omalizumab and dupilumab, I'd appreciate that. Mike?
Dr. Wechsler:
Yeah, so, when patients have elevated eosinophils in the blood or in the sputum or even on bronchoalveolar lavage, an anti-IL-5 therapy can be very appropriate because it's been shown to reduce exacerbations and improve outcomes and reduce oral steroid dosing. And so, what I tend to think of are, first of all: Does the patient have the biomarker? Is the patient eosinophilic? And the thresholds can be different in different individuals. We tend to think of higher eosinophil counts as being more predictive of responsiveness, but even patients who have eosinophil counts as low as 150 cells per microliter may be responsive to some of these anti-IL-5 therapies or therapies that block the IL-5 receptor.

The other factors that I consider, first of all: Are they eosinophilic? Second of all: Do they have severe disease? Are they adherent to their therapy? And then deciding between the different IL-5 blockers can be a little bit of a challenge. There have been no head-to-head studies, as I noted, and so you want to factor in the frequency of administration. Does patient want to come in every 4 weeks or every 8 weeks? Is the patient okay with taking medication at home on his own? Does the patient want to come in to the office? Does patient have a higher body weight that may warrant, perhaps, giving an intravenous therapy that's dose-based on body weight? And then, of course, there are insurance-related factors. Which therapy will the patient's insurance company pay for?

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Dr. Panettieri:
Thanks, Mike, that was very helpful. Jonathan, do you care to comment on omalizumab, who's the right patient for omalizumab and for dupilumab?

Dr. Corren:
Thank you for that very important question, Rey. Omalizumab, as I mentioned earlier, was approved many years ago, in the early 2000s, and has proven that it is effective in patients who have severe, uncontrolled allergic asthma, asthma which is relevantly triggered by something like dust mites, molds or animal danders, and for which the has patient a positive skin test or blood test demonstrating hypersensitivity. Now, many patients do have allergic asthma, and where I think omalizumab has been proven to be particularly successful is in young patients for which there is no other biologic available between the ages of 6 and 12 who do not respond to inhaled standard of care therapy.

We'll move on to dupilumab, a drug which was approved by the FDA for patients with severe, uncontrolled, eosinophilic asthma or patients who are oral glucocorticoid-requiring irrespective of biomarkers demonstrated. Now, if we look at the patients who have eosinophilic asthma, when making a choice on biologics, something that's very important to keep in mind is that comorbidities frequently occur with patients who have severe asthma, the first being atopic dermatitis. Ten percent of asthmatics may have very severe, uncontrolled atopic dermatitis at the same time, and we know that dupilumab has been approved by the FDA for that indication as well. The second indication for a comorbid condition is chronic rhinosinusitis with nasal polyposis for which dupilumab was also approved—in the past several weeks, in fact. So, in patients who have severe comorbid conditions, particularly atopic dermatitis and nasal polyposis, you can give dupilumab and treat both of these very vexing conditions at the same time with the same biologic.

Now, when we look at where dupilumab might play a role in patients who do not have comorbid conditions, I think the important thing to highlight is that efficacy has been demonstrated all the way down to an eosinophil count of 150 with significant effects on exacerbations, so in patients where you're sort of just at the border of documenting a type 2 pathobiology as relevant to their asthma state, dupilumab has been shown to be very effective in those patients, but lest I not say that it's only effective in that group because it's been demonstrated to be effective in patients with lots of exacerbations as well. So I think a patient who has comorbid conditions and has been demonstrated to have type 2 biology may be an excellent candidate for this biologic agent.

Dr. Panettieri:
Great. All right, we're going to come back to you, Amanda. So, Amanda, we heard about the onset of asthma, the difficulty in management, all the items that you received that didn't work, but the good news—right?—the good news, Amanda, is that we found a drug that did work. Can you describe that experience? What was that drug? I believe it was mepolizumab, an anti-IL-5, but what did it mean to you? How did you feel after receiving that drug?

Amanda:
It was a game changer for me. Within a few weeks of the first injection, I felt better. I haven't had to use steroids, haven't had to take prednisone aside from a couple of flare-ups over the last 2 years. My rescue inhaler, I rarely reach for it unless it's a really hot and humid day. I'm able to do things with the kids that I never could before. Last summer we took a trip out to the Grand Canyon and some of the other national parks. We went to Zion, and I was actually able to hike with the kids without having to... Now, granted, I'm out of shape, but without having to struggle for breath, and it was amazing for me. I sleep through the night. I'm not waking up short of breath. My husband sleeps better because he's not worried lying next to me listening to me struggle to breathe. It's been just amazing.

Dr. Panettieri:
Well, wonderful, a wonderful story, Amanda, and a fantastic outcome. Mike, you have the final word here. What do you think? Where are we going with asthma? And if you can comment on Amanda, sort of the classic patient with high T2 inflammation.

Dr. Wechsler:
I think where the future is heading is identification of other therapies, other novel therapies that target, perhaps, different parts of the immune response, both type 2 asthma—and where there is a really big unmet need is non-type 2 asthma, and so therapies that are coming down the pipeline include therapies that target thymic stromal lymphopoietin, or TSLP. There's a drug called tezepelumab, which is very exciting. Other drugs that target prostaglandin D2 receptors particularly for patients with eosinophilic asthma may be coming down the road as well soon. And then I think we need to think about novel biomarkers and novel targets and other novel strategies and think about the patients who got non-type 2 disease and see if we can identify new therapies for those patients. So I'm really excited. I think that... I'm hopeful that my patients and many patients out there who remain poorly controlled will be able to get the right therapy for their specific type of asthma, and so I think this is an exciting time to be practicing asthma medicine in general because of all the opportunities that we have now and the opportunities that are going to merge in the coming years.

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Dr. Panettieri:
Well, I'd like to take this moment to thank my colleagues. Amanda, fantastic job telling your story. I think it's very impactful. Mike and Jonathan, thank you for your wonderful insight.

Now, you've heard about Amanda and Amanda's case. What we'd like to now hear is from you. If you take a moment and fill out the case report form, your case could be selected for discussion by myself, by Mike and by Jonathan. We'd love to hear from you. This is a way of really sharing stories so that this case-based learning can really improve outcomes in a general way. So, very important, please take your posttest and fill out the evaluation so that you can receive your CME credits. Have a good day.

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