Overview: Approximately 12 million children and adults in the US have inadequately controlled asthma, many with severe asthma. Rey Panettieri, Jr, MD, and Nicola Hanania, MD, MS, discuss the importance of and how to differentiate severe from uncontrolled asthma. They review what is known about phenotypes of severe asthma and key biomarkers. Discussion is focused on the evidence for and role of targeted biologics for severe asthma phenotypes as recommended in the 2018 Global Initiative for Asthma (GINA) guidelines. The use of a shared decision-making tool is explored.

Content Areas
- Pathophysiology
- Definition and features
- Phenotypes and biomarkers
- GINA 2018
- Targeted biologics
- Shared decision making

Target Audience
This activity was developed for pulmonologists, allergists, and other clinicians involved in the management of severe asthma.

Learning Objectives
At the conclusion of this activity, participants should be better able to:

- Describe current evidence for the use of biological-based therapies for the treatment of severe asthma
- Differentiate biological-based therapies for the treatment of severe asthma based on patient- and treatment-related factors
- Utilize genetic information to select the appropriate biological-based therapy for a patient with severe asthma
- Apply updated guidance to optimally utilize biological-based therapy in patients with severe asthma

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Reynold A. Panettieri, Jr, MD
Research Support: AstraZeneca, Bristol-Myers Squibb, Genentech, Gilead, MedImmune, Oncoarendi, RFIM, Sanofi/Regeneron, Theratrophix, Vertex
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[ce@annenberg.net](mailto:ce@annenberg.net)

Annenberg Center for Health Sciences

39000 Bob Hope Drive

Dinah Shore Building

Rancho Mirage, CA 92270

Phone 760-773-4500

Fax 760-773-4513

8 AM – 5 PM, Pacific Time, Monday – Friday
Editor’s Note
This is a transcript of Dr. Rey Panettieri and Dr. Nicola Hanania’s presentation “Updates in Precision Medicine: E elevating the Treatment of Severe, Eosinophilic Asthma.”

Introduction

Rey Panettieri, MD: I’d like to welcome you here. I am Rey Panettieri, MD. I’m vice chancellor for Translational Medicine and Science at Rutgers University and I’m joined by my colleague, Nicola Hanania, MD.

Nicola Hanania, MD: Good morning, everyone. I’m glad you woke up early for this. I hope it will be interesting for all of you and I want to welcome you to Texas if you come from out of state. I’m an associate professor of medicine and director of the Airways [Clinical Research] Center at Baylor College of Medicine, Houston. It’s a pleasure to be here this morning and I thank the sponsors and the CME company for putting this together.

Rey Panettieri, MD: Yes. Kudos again to GSK, AstraZeneca, to CHEST, as well as to Annenberg.

We’re going to take you through, in the next hour, the exciting aspect of treating severe asthma. I can tell you—from somebody doing this for 30 years in this space—we have never had a better time to treat our most difficult asthmatics. It’s really an exciting time for what we have to offer but also, and Nick is going to hit this point quite well, concerning the paradigm shift. A paradigm shift, now, moving forward, using biomarkers in precision therapy to manage refractory asthma. I don’t think there’s a time that it’s been better than [this] for treating patients.

Unmet Needs and Pathobiology

Rey Panettieri, MD: Now, how prevalent is asthma? Well, about 1 in 10 in the US population has asthma. It’s incredibly common. Incredibly common. If we look at other important aspects, there are at least 3.3 million children, 9.1 million who have uncontrolled asthma. That’s an incredible number. That really relates to 50% of health care dollars to treat asthma are aimed at that population. Huge medical problem, big prevalence, we need new therapies.

Now when we talk about the immunobiology of asthma, we really look at what cells can we impact. What cells can we impact to improve severe asthma? The target shown is the eosinophil, but in addition, and Nick is going to cover this quite well, the mast cell and the Fc-epsilon receptor, is very, very important.

I’m going to come back to look at specific aspects of the asthma diathesis, the immunobiology, and I’m doing this from the frame point—from the aspect of what you need to know—because it impacts on the phenotype and the therapeutic approach. That is shown in this slide.

Pardon me for making such a crazy busy slide, but it is important to understand non-T2 and T2 inflammation. Now, you all probably remember
Th2. Th2 refers to a very specific T-cell subset. We've now embraced a different concept, that concept of T2 inflammation. It goes beyond. It extends beyond the CD4 T-cell. It extends to the eosinophil, also. It extends also to the ILC2.

Now, these innate lymphoid cells, which have been identified now within the last 10 years, are critical, because they can integrate both T2 and non-T2 signals to induce the asthma diathesis.

Let's talk about T2. T2 inflammation is allergy-driven atopy, mostly eosinophil driven. Eosinophils atopic, T2. Non-T2 seemingly has a signature or an immunologic signature that's remarkably different. Here, what we see is the epithelial cell plays a central role. It integrates damage signals. These damage signals that are alarmants, these are molecules secreted by the epithelium, IL-33, thymic stromal lymphopoietin (TSLP), also IL-25. Then interface and interact to affect function on the innate lymphoid C2 cell.

Now, this C2 cell actually can secret IL-4, IL-5, and IL-13. There's an integration of nonallergen, non-T2 mediated by the epithelium that has some crosstalk to the eosinophil and IL-4, IL-5 to IL-13 signals. Also, the IL-33 can modulate Th17 and affect neutrophil activity as well as trafficking.

What do you need to know? Two big types of inflammation. T2 inflammation, non-T2. Non-T2: Pollutant, bacterial, viral-driven, mostly through ILC2s. The reason that's important is there's going to be new biologics in that space coming out probably within the next 2 years.

Now, let's move over to T2. T2 is going to be eosinophil-driven, atopic, IL-4, IL-5, IL-13 prominent. Guess what? We have biologics in that space.

If you had to say, "Hey Panettieri, tell me, in 100 patients, how many have this and how many have that?" About 60% of patients have a T2 inflammatory signal while 40% don't. With current approaches, we lack therapy for that non-T2, but it is on the horizon.

**Definitions and Features**

**Rey Panettieri, MD:** The definition is shown here, we're not going to belabor this. ERS/ATS got together in 2014 and said, "Hey, how about we harmonize our definition for severe asthma?" As you can imagine, it's uncontrolled asthma despite maximum therapy; high-dose ICS/LABA, another controller plus or minus systemic steroids. Makes sense.

The GINA guidelines which I think is a little crisper than the old NAEPP guidelines, which is dated but is being revised. We know that genome IV and V is where we're going to position monoclonal antibodies. These are patients who, despite high-dose ICS/LABA, require, typically, an antimuscarinic and are refractory to current therapy. It's in that space that we're thinking about the use of monoclonal antibodies, and rightfully so.
Definition of Severe Asthma

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<td>Asthma which requires treatment with high dose ICS plus a second controller and/or systemic corticosteroids in 1 or more of 3 months or “steroid-dependent asthma”</td>
<td>Asthma that requires treatment with high dose ICS/LABA, either oral corticosteroids, or systemic corticosteroids is “refractory” or asthma that remains “uncontrolled” despite treatment</td>
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Now, there are many aspects that contribute to the refractory asthma and I’m definitely preaching to the choir here. You, as practitioners of the art, and specialists [such] as [me], we see that comorbidity over and over and over again. We need to treat the nose and the sinuses to control the asthma, but we can’t forget about smoking as a contributor to refractory asthma. About 30%, 28% of patients with asthma smoke, obstructive sleep apnea, and reflux. Very common comorbidities.

Other contributing factors. As we know, adherence is a struggle and an obstacle and a challenge. Also, inhaler technique and environmental trigger remediation. All told, the deck is stacked against us to treat refractory asthma. We have adherence issues for patients, inhalers that are problematic, so we look for other therapies. Therapies that are going to be parenteral in nature.

Differentiating Severe from Uncontrolled Asthma

1. Asthma treatment requirement
2. History of poor adherence
3. Inability to control or exacerbation

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<td>• Sinusitis</td>
<td>• Poor inhaler technique</td>
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<td>• Vocal cord dysfunction</td>
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<td>• Gastroesophageal reflux disease</td>
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<td>• Medications</td>
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Now, how do we differentiate severe from uncontrolled asthma? Severe asthma is lots of medicines, but not in the ER, not in the hospital, and not requiring oral corticosteroids. Watch the patient’s inhaler technique, identify adherence and barriers, confirm the diagnosis. You are well aware that all that wheezes is not asthma. If possible, remove risk factors, consider treatment step-up, and then maybe refer to a specialist or severe asthma clinic. There, I think, what that offers is therapies like bronchial thermoplasty or other therapies for some patients.

Nicola Hanania, MD: Obviously, uncontrolled vs severe, it’s not usually a dilemma out there for clinicians, and setting the stage very nicely, as Rey did, how we differentiate uncontrolled from severe is very important because while 50% to 60% of asthmatics are uncontrolled, only about 5% to 10% of asthma patients have severe asthma.

Right now, our definition is based on the utilization or need of high-dose steroids plus a LABA or other controllers. Once the checklist that Rey showed is done, the comorbidities, the triggers, the compliance, the adherence, everything, inhaler technique. Why are we concerned about severe asthma? Obviously, the morbidity associated with this.

Many of these patients, as you see on this slide, have frequent symptoms, exacerbations, that’s tied in with the persistent loss of function, lung function decline, impairment, poor quality of life, and many of these patients have comorbidities. While we are lung doctors, we focus on the lung; but, indeed, we have to look at the whole patient. In fact, many of them have significant upper airway symptoms. Many of these late-onset severe asthma patients have rhinosinusitis, polyposis, others have other things. These lead to other comorbidities. It’s the
What have we known and why is it that 5% to 10% of patients, no matter what you do, they're still having symptoms? Well, that really led us to start thinking. Well, thinking outside the box. It's not a 1-size fits all disease. We now know that there are multiple phenotypes for asthma, and many of the factors shown on this slide can contribute to these phenotypes.

There is definitely a genetic link, and there are environmental links. There is the decline in lung function over time—even since childhood—that may contribute to this and, of course, the patient.

What do we know about phenotypes? Well, phenotypes really are clinical description of how patients present to us. They may not be as helpful as what we call endotypes, which are more helpful in defining targeted therapies because they really reflect mechanisms.

Phenotypes are more the clinical presentation of patients and we use the onset of the disease, either early onset or late onset. We also look at biomarkers like eosinophils or allergies to define it. Some of the phenotypes, and these are not inclusive of all what we know, are listed on this slide.

Early onset allergic asthma tends to be very common. That's the classic asthma we're used to from even medical school. Patients start having asthma early on in life as allergy is triggered, has signs of that by their skin testing or blood testing, but the late-onset eosinophilic, late-onset asthma is another phenotype. These patients may not be driven by allergens. In fact, many of them don't have an allergy that triggered asthma. They may have other triggers, but they may present with eosinophilia or also signs of T2 inflammation on biomarkers, which we'll talk about.

There are also late-onset asthmatics who are nonatopic. Many of them are obese, particularly in women. These patients may have minimal airway inflammation, but quite a significant airway obstruction. Then there are the frequent exacerbations. Actually, as it is in COPD, one of the biggest predictors of exacerbation is past history of exacerbation. Those who keep getting oral steroid courses, ER visits, and then, of course, there's another, primarily in women, the late-onset obesity and asthma.
Treatment Overview

Nicola Hanania, MD: Well, let's talk about management the rest of the talk today [is] going to really focus on novel therapies and novel targets, but let's remind ourselves what are the goals of management of asthma. It's not just lung function improvement. It's really more important of symptoms, decreasing impairment, decreased need for rescue medication. Improvement of lung function is important, don't get me wrong, but also, we want to improve exercise tolerance and quality of life but importantly, we want to reduce risk and risk of exacerbation, hospital admission.

Ultimately, we want to reduce hospital admission and mortality. The good news in the United States, at least, mortality of asthma has gone down recently, but we still lose about 3,000 patients a year in the United States from asthma. It's not a large number, but it is a disease that can be treated and controlled and we really need to strive [to see] how can we prevent or reduce this even further.

Well, there are several goals when it comes to severe asthma, and this is really focused. There are several buckets as you see on this slide. I'll try to go through these quite quickly so that we can talk more about what's new out there.

![Management of Severe Asthma](image)

Obviously, one of the very first things you want to know when it comes to pharmacologic therapy is to optimize inhaled steroid and controller therapy. That's very important. Make sure the patient is taking their dose and going up on the inhaled steroid—that can help—although there are multiple studies now showing [that] in patients who are in impending exacerbation, doubling or quadrupling inhaled steroid does not really do it and that some of these patients need other things.

I'll briefly talk about oral steroids in a minute, but there are other potential therapies that need phenotyping. We'll talk about how we do it with the biomarkers we have these days, and then there are obviously nonpharmacologic therapies.

Add on, without phenotyping, are other certain medications, where I don't need to phenotype patients, where the [medications] work. I think one of the recent additions to the armamentarium we have are the long-acting anticholinergics in addition to the inhaler steroid LABA. These are important drugs that have been shown in multiple clinical studies that you don't need to have . . . They don't just work in eosinophilic or allergic—maybe you don't need any phenotyping.
What about oral steroids? We all know the horrible side effects [of] oral steroids and indeed we are really . . . We strive in our clinics, and I'm sure you do, to try not to use oral corticosteroids. Indeed, when you look at the different guidelines, whether the NIH guidelines, the ERS/ATS guidelines or the GINA Strategy for Management of Asthma, I won't read this, but they all really warn us about the side effects of oral corticosteroids. They all advise us to use the minimal dose possible and to monitor for side effects.

Indeed, there are several papers, one just recently published in the *Journal of Allergy and Clinical Immunology*, these are from claims data analysis, large cohort observational, obviously. But looking at even patients who need 4 or more courses of oral steroid in the preceding year and they looked at comorbidities associated with this. We think that only patients on continuous oral steroids have problems. Actually, in that analysis, it showed that even 4 courses a year was linked to an increased odds ratio of having several of the comorbidities associated with oral steroids. Keep that in mind, when you see these patients who require regular courses of oral steroids to control the disease, or those on continuous oral steroids, to look at other avenues. What can I do for that type of patient?

There are certain treatments where we need to do phenotyping, which I'll talk about in a minute. But before that, I want to mention an important nonpharmacologic approach in some patients, although we still have not identified that phenotype who would respond best, is bronchial thermoplasty. And obviously, managing other comorbidities such as depression, anxiety, and other things that can be done nonpharmacologically as well.

What about the phenotyping? There are strategies using a sputum-guided approach. Obviously, that's good, but not very practical. It's been shown that if you measure sputum eosinophils, and escalate the dose of inhaled steroid or start something that targets that, you have a better outcome than just using your clinical sense of control or assessment of control.

Phenotyping has been something that we are pushing, but to do so really rightly, you need some biomarkers, tools that you can use in the clinic. Nobody expects us to do sputum induction in every patient, although in some specialized centers they do. We really need something practical to measure, and biomarkers really are important.
Now, we're very, very early in that field because we only have a few biomarkers, all of which reflect what Rey mentioned, T2 airway inflammation. We don't have good biomarkers that reflect the non-T2 asthma.

Some of the biomarkers we use, although the last one, periostin, is really in research right now, it's not available for us to use. But some of these biomarkers have been utilized actually to look at more targeted therapies for asthma. IgE, obviously, is important to identify allergic asthma. Although the level of IgE is not a good predictor of effect for anti-IgE therapy, it is important to measure to not only dose, but to predict who would need an anti-IgE therapy.

We'll talk a lot about eosinophils in a few minutes. Blood eosinophils have been shown to correlate nicely with sputum eosinophils in the proper context. I have to preface this, because there are lots of issues with blood eosinophil. When to measure them, how often, due to their confounding effects.

Neutrophil sputum is not really a very good biomarker, and actually it's not really the best to identify non-T2 asthma. Exhaled nitric oxide is reemerging. It's an important biomarker. It's a very good T2 biomarker. It's not only predictive, but it has a prognostic effect just like eosinophils do. The higher the FeNO at baseline, the higher risk of exacerbation, but also it is a good predictor of response to certain agents like inhaled corticosteroids, but also drugs that target IL-13 pathway. It's also a pharmacodynamic biomarker. The levels of it come down with treatment like with inhaled steroid, with drugs targeting IL-13. It is not effective with drugs targeting IL-5. Periostin is still in the pipeline. Whether it comes to fruition, that we can use in the clinic, it's still unknown, but it's a very good serum biomarker that reflects IL-13 activity.

We have toyed around whether such biomarkers can reflect response and one of the very first papers we published was an exploratory study looking at our data from the EXTRA study, which was looking at the effect of omalizumab in reducing exacerbation. Indeed, at that time, this was published many years ago, we showed that some of these T2 biomarkers actually, indeed, reflect, if they are high, reflect better effect from anti-IgE therapy. Omalizumab in here. You can see the FeNO, high blood eosinophil, and we did have some patients where we measured serum periostin.

Do they stand up, this type of thing or predictors, in real life? Well, with omalizumab, a more recent study, a real-world study, actually did not show that eosinophils really predict response to omalizumab therapy. In this French study, this was an observational, real-life type of study. They showed that whether the eosinophils were
high or low, the effectiveness of omalizumab was similar.

We need to do more studies on biomarkers to predict, or at least define, their exact role when it comes to targeted therapy in asthma.

Talking about targeted therapy, we’re going to shift gears now to talk about specific drugs. What do we know and what do we have right now and what may be coming? You can see that some of these biomarkers are approved, the anti-IL-5s. Dr. Panettieri is going to talk about IL-5 and I’ll [talk] a bit about dupilumab which is an anti-IL-4 receptor which is not approved yet but may be soon. [Editor’s note: Dupilumab was approved in the United States for selected patients with moderate-to-severe asthma on October 19, 2018.]

We want to talk today about another biomarker and another targeted therapy, tezepelumab, which is an anti-Tslip. It is in phase 3 trials. Then there is this small molecule, not really a biologic . . . fevipiprant, which is a DP2 antagonist also in phase 3 trials, which may be coming hopefully for patients and for us to use.

What do we know about these biologics? As you see here, I won't go through the details of this table, but we are going to focus on these approved drugs today, mostly, and show you what are the clinical data, the safety, the efficacy, of these agents. You see the approved indications in this table.

**Treatment Omalizumab**

Nicola Hanania, MD: Let's start with targeting IgE. Omalizumab has now been used for more than 15 years. In fact, IgE is an important biomarker to define probably allergen-specific IgE is much better than total IgE. It's actually definitive to define allergic phenotype.

Now, the level of IgE is important to define the dose we need to target patients with allergic asthma, but it's not a predictor for response. It's important to keep that in mind. What we know is that omalizumab targets circulating IgE and thus it blocks IgE and prevents it from tagging on
the Fc-epsilon receptor and thus, release of mediators from the mast cells.

Well, this was a simplistic thought that we had, but now we know that anti-IgE may have other effects including the decrease in Fc receptors on other inflammatory cells, but there are some good data, emerging data, that they may have effect on viral clearance and, thus, may reduce viral-induced exacerbation, but also may have some effect on, actually, the incidence of asthma. It’s been now tested in a large NIH study.

One of the studies we performed with the omalizumab was a large US study on patients who are uncontrolled asthma with a history of exacerbation. We found that patients have 25% risk reduction in exacerbations when omalizumab was added to high-dose inhaled steroid and LABA. Also, in the same study, we also looked at asthma quality of life and we looked at the biomarkers which I just showed you earlier.

There are lots of questions with anti-IgE. How do I know the patient is responding? How long do I keep them on? Do I really need to keep giving the patient every 2 weeks? It's either every 2 weeks or every 4 weeks depending on the IgE level. These questions are still not fully answered, but I think we are working on them.

It's going to still be there. Obviously, many of the allergic phenotype patients also have eosinophilic phenotype. The question that always comes to mind and, including myself, what if I have somebody with allergic asthma who has high eosinophils, do I use something that targets eosinophil or do I use an anti-IgE or maybe in the future a combo type of drug may be needed? It’s something that may need [to] be explored further.

To summarize, what we know about anti-IgE is that there is definitely the effect on reducing exacerbation, improving quality of life, and there are studies showing decreased health care utilization. The studies that were done on less severe patients than those done with anti-IL-5, if you look at meta-analysis, there is an effect on reduction in oral steroid dose, but it was not systematically studied as [were] the studies that were done with anti-IL-5 in large trials. There's been lots of safety studies, long-term studies, and also real-life safety studies as well.
Well with that, I'm going to shift gears to Rey and he's going to walk with the eosinophilic asthma and what do we know about it and how do we target eosinophilic asthma.

Rey Panettieri, MD: Great job, Nick. I really appreciate it. He just covered 15 years of monoclonal antibody therapy in severe asthma as we know it. I think I want to highlight a couple of items that Nick mentioned that are really important. What is the workup that you need to do for severe asthma? You need to do really 4 tests. You need to measure your eosinophils in the periphery. You need to measure total IgE. You need to measure specific IgE and I'd also say, FeNO is going to be very helpful in discriminating patients that we may choose to treat.

The other concept that Nick brought out which was really important for you to understand is something called pharmacodynamic markers. A pharmacodynamic marker for you, as a clinician, means I engage a target and I know the target's been engaged. Well, what do you mean? Well, if I take an antibody that wipes out the eosinophils in the periphery and I measure a blood count before I give the antibody and after, and the eosinophil goes away, I know I've engaged a target. Now, I didn't answer the question: did asthma get better or not? But I know the target's engaged. Then I ask the question: did symptoms improve, quality of life, functional status, FEV1, exacerbations? Why is that important?

Well, if I took out all the eosinophils and none of those other outcomes worked, guess what? The eosinophil is not a major component to that patient's asthma. We have no other drug, as pulmonologists, that allows us to determine pharmacodynamics markers, typically. This is a really hot time.

Treatment: Mepolizumab/Reslizumab/ Benralizumab

Rey Panettieri, MD: Eosinophilic asthma, about 40% to 60% of asthma, is eosinophilic. Remember what I mentioned? T2 inflammation being about 60%? There's an alignment. Eosinophilic asthma, as more eosinophils are higher, people tend to have more hospitalizations and ER visits. IL-5 is essential for the happiness of an eosinophil. If you remove IL-5, the eosinophils are not happy and they die. That is a target.

There are ways to target IL-5. There's a circulating IL-5 and the antibodies that attack soluble IL-5 in the body is mepolizumab, reslizumab. They bind the ligand. Once bound, it prevents it from activating the receptor that lives on the eosinophil and the basophil, by the way.

Another approach, different mechanism of action, is to have the antibody bind directly to the IL-5 receptor on the cell. Now, that antibody, benralizumab, has a neat tail that is fucosylated
which allows natural killer cells to come in and kill the eosinophil. It doesn’t spew its contents. It just simply implodes and dies a quiet death. The whole point here is there’s different mechanisms of actions whether they impune different efficacy, we don’t know as of yet.

Now, one of the first studies ever using a monoclonal antibody in humans was done by Leckie and colleagues and this is going back to the beginning of time—Lancet, 2000. What they did is they gave mepolizumab to patients prior to an allergen challenge, 3 allergen challenges.

Placebo, notice what happens to the blood eosinophil count. You give an allergen challenge, eosinophils go up. Of course they do because they’re sensitive and the eosinophil is an important cell in modulating atopic or allergen-induced bronchospasm.

In those patients treated, those patients treated with mepolizumab, look at that. The eosinophils that started high, were nearly obliterated. They didn’t go all the way down to nil, but you can see there’s no more peaks with allergens. This was one of the first studies ever to target a cell and remove the late-phase response of asthma with an anti-IL-5.

Now, the Leckie study that then moved on into clinical practice failed in its primary outcomes, failed in improving exacerbations. This is a good example of a good drug for a wrong patient because they took all comers. They didn’t just look at severe asthma. They didn’t just look at exacerbates. When they took it to all comers, there was no demonstrable difference in functional outcomes and that really cause the pause as to whether this is an important drug.

When redefined in the right patient at the right time, mepolizumab was really quite effective, and that’s shown here if we look at Param Nair’s study and looking at mepolizumab. This is a subcutaneous 100 mg dosing of an anti-IL-5 currently available. In this study, they looked at severe prednisone-dependent eosinophilic asthma. Notice patients without exacerbations. A lower score is worse. What you can see, this is baseball or football, not golf. What you see, placebo. These patients had lots of exacerbations, but with mepolizumab, you had improvement in the exacerbations. That led to other studies with mepolizumab and looking at exacerbations of refractory eosinophilic asthma.
Now looking at cumulative exacerbations. Placebo, lots of exacerbations. Look at mepolizumab. Mepolizumab now in patients with exacerbation history and a strong component of reversible disease, you can see that it markedly diminished exacerbations. These early studies were curious because there was no change, actually, in the early studies in some of the other markers that we would have thought important, like the FEV1, or even in this point, the methacholine challenge as determined by the PC20. We still didn't quite get the right group of patients that we focus on therapy.

On came Ian Pavord’s study published in The Lancet. This was a dose-ranging study using 3 doses and using exacerbations as a readout. Now, you’re seeing a definite drop in exacerbations. They found the signal, getting it to the right patient at the right time, and what's curious is all 3 doses were equally effective.

Two studies were done, the Ortega study published in The New England Journal of Medicine in 2014, followed by Elisabeth Bel's glucocorticoid-sparing study, and you can see again, now IV to the subcutaneous, this is the approved dose that you all are using right now. You can see whether it was IV or subcutaneous, equally effective in decreasing exacerbations. And when there was a refinement in who you gave the drug to, that is people with large reversibility components in their FEV1, now you saw improvement in the FEV1.

Further, those patients who are on baseline oral steroids, you could drop the dose of oral corticosteroids nearly 50% when people were on mepolizumab and, as important, what you can see is dropping your oral dose still providing the patients with substantial improvement in exacerbations.

What I did here is take you through the history of big pharma trying to figure out the right drug for the right patient. We, in our practices, have to do the same thing. We have to find the patient where we can say across the table with 75% certainty, "You're going to respond to that drug."

That's the mepolizumab drug discovery and clinical development. We have it in practice. We now are using it for about 4 years, subcutaneous monthly dose.

Reslizumab, another anti-IL-5 antibody that targets soluble IL-5 is an IV formulation exclusively. The uniqueness of reslizumab is its body mass index (BMI) dosed. In this case, you
can tailor it to weight. It is an IV formulation. This is their clinical development. Early phase 2 studies looking at FEV1 improvement, 16 weeks with the duplicate study, then the paired registration studies that were exacerbation, and then the long-term safety studies.

If you looked at the IV dosing of reslizumab in patients with high eosinophils, what was seen is as you step up the peripheral eosinophils in individuals, you find a marked improvement in the FEV1 with an improvement in quality of life measure as shown here as the ACQ-7.

Another important take away—eosinophils matter. If eosinophils are present, target using an anti-IL-5, but another lesson to be learned is the higher eosinophils, the greater likelihood of a response. That has occurred in 3 different drugs from 3 different pharmaceutical companies all demonstrating the higher the eosinophil, the more likely the response.

What’s the breakpoint? At 300 seems to be critical, 300 and greater, more likely to respond. If you’re 700, gee whiz, this could be a life-changing event. Under 300 you may be in a coin toss. We need to be careful in the under 300. Over 300 is a good metric.

If we look at the efficacy of reslizumab in poorly-controlled eosinophilic asthma, and Nick had defined what poorly controlled was, you can see now the improvement in ACQ markedly improved with reslizumab vs placebo. Of course, placebo had an effect as [it] does with every clinical trial in asthma. There’s a placebo effect because people start taking the medicines they were prescribed.

If you look at exacerbations and lung function, again, probability of having a clinical asthma exacerbation, placebo and reslizumab, dramatic improvement. Also, the IV formulation markedly improves the FEV1 over placebo.
When you look at the exacerbations and look at it whether required systemic steroids, placebo, reslizumab, in all cases diminished exacerbation rates.

Now let's move to the antibody that attacks the IL-5 receptor, that's demonstrated here. What's being demonstrated is the IL-5 receptor is the target. When benralizumab binds to that through an alteration in the long chain of the immunoglobulin, the natural killer cell binds to it and through performance and granzymes actually cause the implosion of an eosinophil. This approach, which is antibody-directed, cell mediated cytotoxicity is unique for this drug in the asthma space. Other monoclonals have a very similar phenomenon in rheumatoid arthritis, but suffice it to say, the take away, reslizumab, mepolizumab, attack the ligand that circulates. Benralizumab attacks the receptor.

If one looks at the annual exacerbation rates here at an every 4 weeks or 8 weeks benralizumab, approved drug, you dose monthly for 3 months and then every 8 weeks, which is a convenience. You can see a decrease in exacerbations in patients with greater than 300 and some benefit even with under 300. Recognize, I mentioned 300 was the cutoff. If you're 250 or 299, you would have fallen into this bucket.

Now, this was a wonderful study done by Nair and colleagues looking at the oral corticosteroid dose. What they did is a very long run-in, being sure that the patient was steroid-dependent and then tapered their steroids. You could see in the first 8 weeks, you could taper everyone's steroids almost by 50%. When patients were on drug, either benralizumab every 4 or 8 weeks, what you can see is that they had a sustained drop of 75% of their oral corticosteroid dose, whereas placebo could not be sustained and had to pop back up because of refractoriness to their symptoms. The take-away message here, this drug vs placebo can decrease oral steroids by 75%.
It also extended the time to the first exacerbation shown here. Placebo, benralizumab and you can see the time to first exacerbation was very much pushed down.

Now, this is an interesting and provocative study. What Mukherjee did here is say, "Okay. We're looking [at] people on mepolizumab," and then after a period of time switched them to reslizumab. Now, this is not a comparative efficacy study, so please don't take that away here. This was published in the American Journal of Respiratory [and] Critical [Care] Medicine. They got mepolizumab, they looked at specific outcomes, switched over now to reslizumab BMI dose to IV, and compared to placebo.

What it showed was interesting. If you're looking at sputum eosinophils, pre-mepolizumab, post-mepolizumab, there was a trend numerically in a decrease in the sputum eosinophils. If you look at pre-reslizumab, placebo, no difference. With reslizumab IV formulation, the central hypothesis was if I give this IV, I'm going to affect different compartments than the circulating subcutaneous given mepolizumab, and you can see here the eosinophils were annihilated. If you look at blood eosinophils, pre-mepolizumab, post-mepolizumab, went down. Again, you saw a substantial decrease.

Now, if you look at a variety of provocative markers, not only the presence of the eosinophils, but the activity of the eosinophils, he made the point pre-, post-mepolizumab, not a lot of change in the enzymes secreted by eosinophils. But after reslizumab, there was a dramatic drop, as well as seeing with another marker of eosinophil activity. Now, in this study it was not powered to compare exacerbation efficacy and there was no difference in the FEV1. This was a provocative trial looking at biomarkers to determine differences.

What I want to leave you with is the IL-5 therapy today is essentially a human knockout of the eosinophil. We think of knockouts in mice. But we're saying these antibodies are so effective that they could obliterate the eosinophil in the body. To answer the question, you need to know: does the patient's asthma get better?
Treatment: Dupilumab

Nicola Hanania, MD: We're going to talk about dupilumab, which is a drug not yet approved, but it's in the hands of FDA now, maybe soon to be approved. [Editor’s note: Dupilumab was approved in the United States for selected patients with moderate-to-severe asthma on October 19, 2018.] What dupilumab does, it actually blocks IL-4 receptor-α. For those who don't know, IL-4 receptor-α is a common receptor for both IL-4 and IL-13. We have previously tested anti-IL-13 in large clinical trials. Unfortunately, 2 molecules have been looked at, utheralizumab and lebrikizumab. Unfortunately, targeting IL-13 alone did not really make the mark in consistently reducing exacerbation. With this drug, because it targets the IL-4 receptor, it actually targets downstream, signaling of both IL-4 and IL-13. To understand what potentially can happen, you really need to understand the effect of the cytokines. IL-4 is a very important mediator because it actually helps in Th2 differentiation and IgE production. It's a very unique mediator to do so.

IL-13, on the other hand, is one of the effecter cytokines. Like IL-5, it's very important. Eosinophilic recruitment is 1 of its functions, but, also, it may have an effect on mucus production, as well as possibly airway remodeling and structures of the airway.

Now all this is hypothetical, based on in vitro studies on human cells, and certainly no studies were done in vivo, not yet at least. What went off from the clinical trial is targeting IL-4 receptor may actually have a beneficial effect in patients with high risk of exacerbation. This study was published actually during [an] ATS meeting, by Mario Castro. Looking at [the] large study, 1900 patients with uncontrolled asthma, they did not specify . . . they all had to have [a] history of exacerbation . . . but they did not specify that they have high blood eosinophilis, although they measure these biomarkers. Exhaled nitric oxide was measured as well.

To understand this slide, you can see that they've tested 2 doses. The 200 mg every 2 weeks is given subcutaneously and also the 300 mg every 2 weeks. Naturally, they had 2 placebos because of the volume of the medication. That's why you see 2 placebos and 2 doses of the drug. The bottom line over the 1 year of the study, the reduction of the exacerbation was significant in the ITT population. Sub-analysis of this showed that the higher the blood eosinophils, but also the higher the FeNO, the better the response to this type of drug. It's a drug that targets T2 inflammation and it also improves lung function. Indeed, actually, when you look at lung function improvement, it's pretty quick. Within 2 weeks you can see improvement in lung function that is sustained all throughout the 1-year study, compared to the placebo arms.
Another study published in the same issue of The New England Journal of Medicine, the Adventure Trial. This was a very similar study to the ZONDA study that Rey discussed with us. It was a steroid-tapering study in patients who are steroid-dependent. Again here, like the ZONDA with benralizumab, this is with dupilumab. This drug was also successful. The higher dose is what was used here, every 2 weeks, was able to get people off prednisone. There was a placebo effect as well, but this was statistically significant. Then on the right side, you can see the steroid dose reduction in 48% of patients were able to come off prednisone.

Having seen these data, the efficacy and the safety of all these biologics have been pretty consistent and in general, they're fairly safe. With the anti-IL-5s there are now data up to 4 years in multiple studies. Some of them were presented at ATS, suggesting that they are pretty safe. With dupilumab, we have 1-year data and long-term safety study is ongoing. There were some patients who had raised their eosinophil count. As opposed to anti-IL-5s, blood eosinophils may actually go up with treatment with dupilumab early on and then they are sustained. This drug may prevent recruitment of eosinophils to the airway, but blood eosinophils may go up after treatment, as opposed to the anti-IL-5s.

We've gone through a whole a journey of clinical trials with biologics and more to come. I think one of the major shortcomings of these trials is that we only have limited data. Right now, we have 1-year data on dupilumab, 4-year data on mepolizumab and reslizumab. We don't know the exact biomarkers. There's quite a bit of overlap between the biomarkers predicting response to one drug vs the other. We don't have [a] good algorithm to us, as clinicians, which one should we try first especially when it comes to overlapping phenotypes, and definitely we don't have data on combination therapy. I think this probably ultimately needs to be done, because even with the best biologic out there, you still have about 15% to 20% of patients, no matter what you give them, they still have an exacerbation. Even despite the fact that these drugs can reduce exacerbation, they don't put the point back to zero. There's still a need, and possibly, combination biologics, like our colleagues in oncology do, may be ultimately needed if we want to target more than 1 pathway.

Limitations of Major Trials for New Biologics

The major trials for new biologics had limitations, including:

- Small sample size
- Additional studies with larger groups of patients are needed to confirm findings
- Short treatment period
- Limited data on durability of response exist
- Determination of most effective biomarkers to select responsive patients is still an unmet need
- Limited data on which biologic to try first
- No data on combination therapy with two biologics

Shared Decision-Making/Conclusion

Nicola Hanania, MD: Before I conclude with the post test, I wanted to remind you if you haven't heard, but we worked with the CHEST Foundation and with the American College of Allergy, Asthma, and Immunology to design this tool which is online on the CHEST website and the American College of Allergy, Asthma, and Immunology website. It's a shared decision-making tool for patients, because patients should be able to have shared decision when they choose a biologic. Obviously, they're not physicians, but they need to read about these biologics, they need to understand this is a commitment, they need to know what to expect, how safe these are. This is a tool that we have developed and it is available for patients to
browse through before you make a definitive decision which drug to pick for them.

Currently, novel targets are being identified. We shared with you what we know and what we have right now, and what is on the way very shortly, but there are several others being tested. I think the nice thing about it is now we have a better look at asthma that it is not one disease, it's actually a spectrum of diseases. It is quite heterogeneous, and I think if we really need to do a precise approach to therapy, we need to subdivide these patients, and also have the appropriate tools to do so, like biomarkers, which is something that now we are working on, and other people are working to define. I'd like to thank you for your attention and I would like to urge you to take the posttest question that I'm going to go through and then we will open it up for a question and answer period. Please, these are the same questions that you've seen before. It is very important for the organizer to know if there is any benefit from what we have talked here about today, so this is the post-test.

In conclusion, what Rey and I tried to convey to you today is that in the year 2018, we have a new look at asthma and certainly, most asthmatics are well-controlled if they are compliant with medication, use their inhaler correctly, and their triggers and comorbidities are measured. Yet, we have about 5% to 10% of patients who need more than the standard therapy.
References


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