Advancing Knowledge to Practice:
Optimizing Severe Asthma Care
in the Age of Biologics

OVERVIEW

Michael E. Wechsler, MD, and **Jonathan Corren, MD,** discuss the clinical differentiation of asthma subgroups and the characterization of inflammatory pathways, as well as biomarkers for severe asthma and their application in clinical practice. They review the latest treatment options, focusing on new biologic-based targeted therapies, differentiating between biologic agents and their mechanism of action, as well as the latest safety-and-efficacy data of targeted therapy. They also discuss optimal treatment regimens based on asthma severity and biomarkers.

CONTENT AREAS

- New biologic targeted therapies
- Optimal treatment regimens
- Potential of combination therapy
- Biomarkers
- Novel emerging therapies

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CE STATEMENT

Target Audience

This activity was developed for pulmonologists, allergists, primary care physicians, nurses, nurse practitioners, and other clinicians involved in the management of severe asthma.

Learning Objectives

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

- Explain how phenotypic, endotypic, and other genetic characteristics factor into severe asthma
- Compare and contrast biological agents that are currently available or emerging in the treatment of severe asthma
- Identify patients who may benefit from the use of a biological agent for severe asthma
- Employ a stepwise approach to incorporate novel, personalized biologic-based treatment plans for severe asthma into the real-world clinical setting

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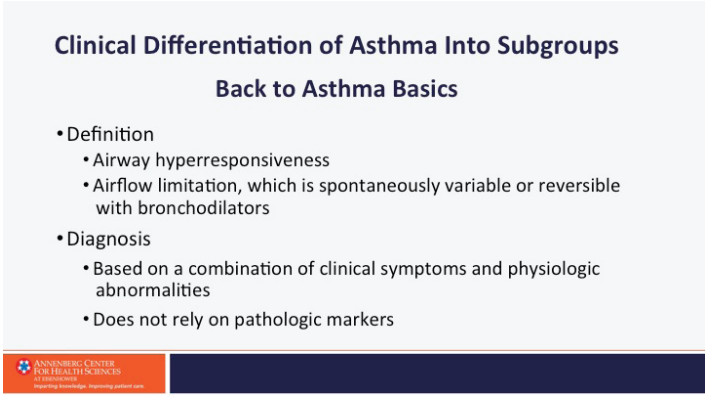
Phenotypes and Biomarkers

Jonathan Corren, MD

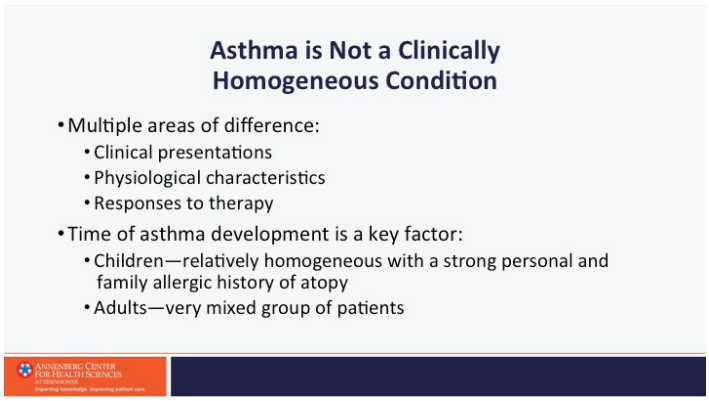
We are going to be discussing how phenotypic and endotype and underlying pathogenic mechanisms factor into the evaluation and treatment of severe asthma. We will review the clinical differentiation of asthma subgroups and the characterization of inflammation, pathways and certain biomarkers, as well as its application to clinical practice.

Let's start with the concept differentiating asthma into subgroups. In order to do that we have to take a step back to some of the basics regarding, what is asthma? We'll start with the physiologic definition, which is really the main underpinning of how we diagnose asthma in the clinic. First of all, there is airway hyperresponsiveness. In the real world, we may experience this by breathing in cold air and developing bronchospasm. In the laboratory, we use something called methacholine challenge to make this diagnosis precisely. Along with this, we see airflow limitation, which—generally speaking—in an asthmatic is a spontaneous event. It happens with, virtually, a variety of different triggers. And it will either spontaneously resolve, or it may need to reverse with a pharmacologic agent, like a bronchodilator.



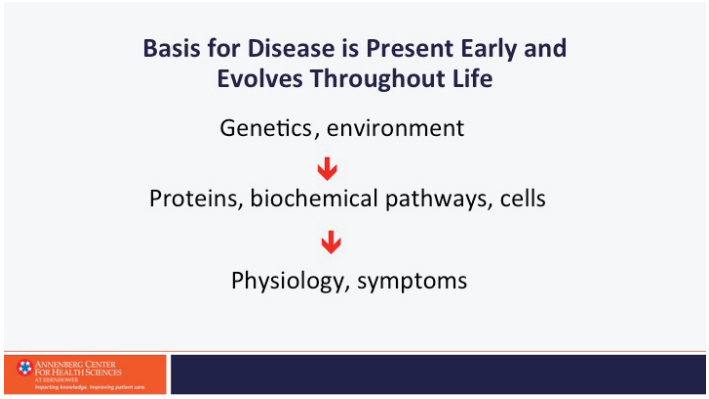
If we move on to taking some of this physiologic background into the diagnosis, it's based on a constellation of different symptoms, and some of the different diagnostic tests that we've talked about up to this point. One thing to keep in mind, and something we've learned very well over the past decade, is that asthma is not a clinically homogeneous condition. There's a lot of differences between various patients, in terms of clinical presentation, in terms of their physiologic characteristics. One patient having very severe bronchospasm, another very mild. And then, finally, how patients respond individually to different forms of therapy, particularly inhaled glucocorticoids.

The time of asthma development seems to be a key factor in sorting out this process. Very young children tend to be relatively homogeneous with regard to how their disease presents. In other words, they tend to be allergic, they tend to have a gradation of airflow limitation, whereas in adults, it's a very, very mixed bag—is what you find both clinically and physiologically.

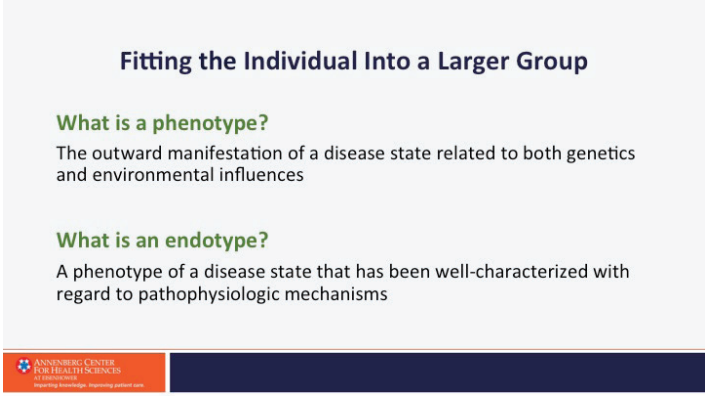


The idea of heterogeneity asthma is not a new concept. In fact, I was able to identify an article going back 42 years written by Sheldon Spector and Dick Farr, published in the *Journal of Allergy and Clinical Immunology*. The title of the article is "The Heterogeneity of Asthmatic Patients—an Individualized Approach to Diagnosis and Treatment."[1] And this was the first time that someone had actually made the remark that asthma may have many different faces in how we approach it, and how we treat it.

Something that we have to keep in mind is that many of these different factors begin very early in life, and they evolve as the person grows older. Genetics plus environment is something that occurs from the very onset of life. And based on these 2 factors—the interaction of the gene and the environmental factors—a variety of different proteins and biochemical pathways and cells, particularly inflammatory cells, will be wired and programmed to come out at various times in a person's life. Ultimately these proteins and pathways and cells will result in a change in the person's physiology, potentially with bronchospasm, as well as symptoms. The symptoms that we call bronchial-asthma.

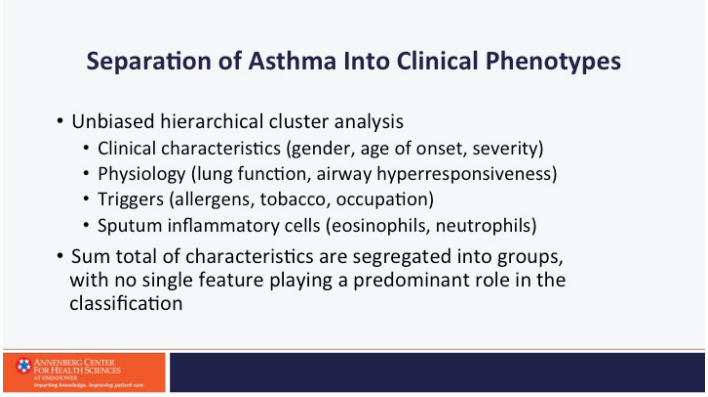


One of our tasks as we try to generalize how a patient fits into a larger group is, first of all, define some of the key terms. First, what is a phenotype? A phenotype is a term we use frequently, and we all understand it to be an outward manifestation of how a disease state presents as a combination of genetics and environmental influences, as we mentioned earlier. But a term that you may not be familiar with is that of endotype. A more recently coined term, which refers to a phenotype of a disease, wherein we have a very good—or think we have a very good—understanding of what the underlying pathogenic mechanisms really are.



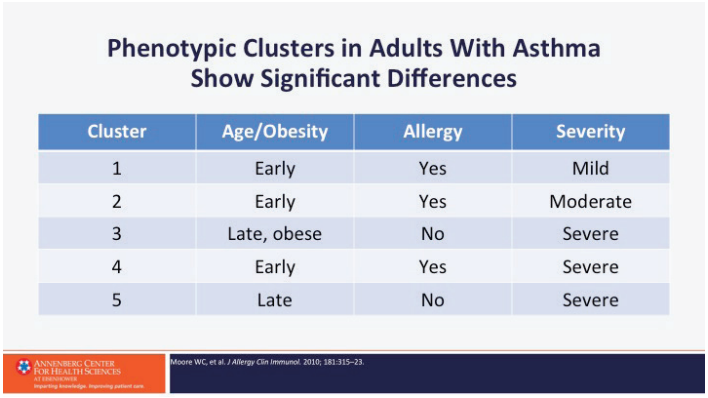
It's now incumbent upon us to look at some of the data over the past decade and try to understand how we can separate asthma into clinical phenotypes. If you go back more than a decade ago, oftentimes we spoke of asthma as either being an allergic disease or a nonallergic disease. But then a group of investigators at the Severe Asthma Research Program,[2] comprised of a large number of academic centers throughout the US, decided to take a different approach. In that they took an approach called Unbiased Hierarchical Cluster Analysis. Where you may take 50 different features, or even up to 100, and pour them on to the table, and see how they segregate in a large group of patients, typically 1000 or more.

And some of these characteristics, we've touched on already, would include clinical characteristics, ranging from gender to age of onset of the disease, or even the severity of the disease. The physiology. And here we're referring to lung function or some measure of airway bronchial, airway hyperresponsiveness.



Triggers of asthma can include things like allergens, like cats and dust mites and pollens. Tobacco—a very onerous trigger that may ultimately result in permanent airway obstruction. And even the kind of occupation that a person pursues. And then, finally, sputum inflammation. Looking at cells, both the eosinophils and neutrophils, in an attempt to characterize what kind of a pathway is most involved in that person's individual case of asthma. When you take all of these different characteristics, and you segregate them into groups, with no single feature playing a predominant role, you get a more balanced view of what that patient's clinical phenotype is comprised of.

What we're looking at now is the first publication that came out of the Severe Asthma Research Program, Hierarchical Phenotypic Clustering,[3] where they looked at adults with asthma and showed that there were 5 different groups that asthma could be broken down into: based on age, presence or absence of obesity, the presence or absence of allergy, and finally, the severity level of that patient.



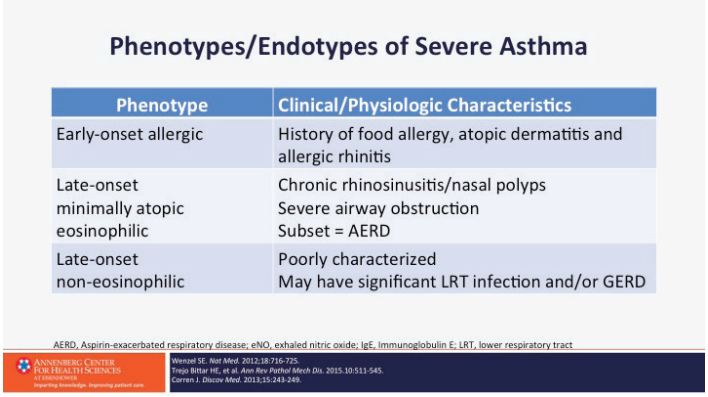
In Cluster 1, it was an early-onset disease: very allergic and mild in nature. Second group was also early onset: also allergic, but more moderate, requiring more medication in order to control the disease. With Cluster 3, we now reach the patients who actually have severe asthma. Cluster 3 being a group of late-onset, obese patients, the majority being women, who are not very allergic, and had very severe disease. Cluster 4: early onset, highly allergic, and very severe. And then finally the fifth cluster, which most people would consider to be the most difficult to treat, with the worst outcomes, being a late-onset form of the disease, minimally allergic, with a very high level of severity.

When we turn to children, the clustering tends to be a little bit different. I touched on this issue earlier when I said children tend to have a more homogenous picture. And throughout the United States, as well as attempts in Europe when they tried to cluster children with regards to their asthma, they're all associated with current or history of atopic dermatitis, and an elevation of their total or specific allergen related [Immunoglobulin E] IgE.

And this is a continuum. Where the continuum really is based on the number of controller medications, their level of lung functions, and their exhale nitric oxide concentrations. But, by and large, they don't really differentiate as much as the adults with asthma.

What I'm going to show you now are really our attempts to endotype, what we consider to be some of the key groupings of patients who do have severe asthma. Group 1 being that which we saw earlier, an early onset form of asthma. And again, keep in mind that these 3 groupings all have severe asthma. These patients usually have a history of food allergy, most likely egg or milk. They may have had atopic dermatitis, very commonly. And, finally, they'll develop allergic rhinitis and or conjunctivitis before finally developing asthma.

The next grouping we call late-onset, minimally allergic or minimally atopic eosinophilic asthma. These patients have



a form of disease that often follows a severe bronchial infection, followed by the onset of recurring sinus infections. When these patients are examined, they frequently have chronic rhinosinusitis with nasal polyps. They tend to have more severe airways obstruction than any of the other groups we've looked at. And there is a subset called Aspirin-Exacerbated Respiratory Disease (AERD), where patients have all of the above features, but in addition to that, they also have an exacerbation of their nasal obstruction or asthma in response to things like nonsteroidal anti-inflammatory drugs.

And the final endotype would be late-onset non-eosinophilic. This is more defined by what it's not than what it is. What it's not, is we don't find markers of eosinophilia, we don't find markers of IL-4 or -13, such as exhale nitric oxide. And, typically, these people may have the involvement of chronic or recurrent lower respiratory tract infections and gastroesophageal reflux disease.

The discussion that we've been having about phenotypes and clusters of asthmatics takes us to the next topic, which is really to characterize better the inflammatory pathways and biomarkers that we use to differentiate asthmatics clinically. We're going to break it down very simply into 2 pathways of asthma: the first being what we call type 2, previously called Th2 or T2 type of asthma, which comprises about 50% to 70% of all patients. The other being a non-type 2 pathway, which includes the other 30% to 40% of asthmatics.

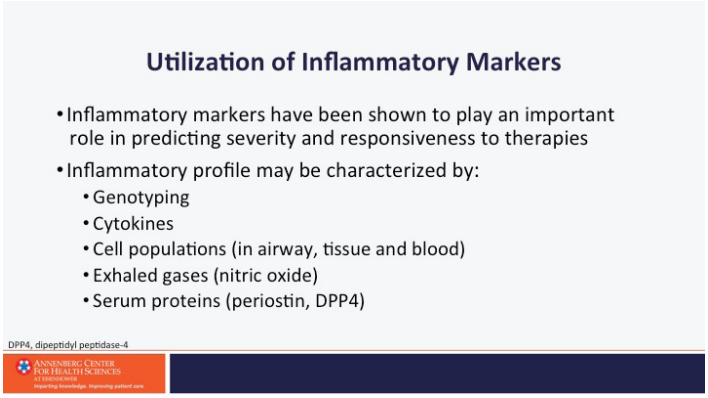
We'll start with an issue of cytokines. The cytokines in type 2 asthma are typically characterized as being interleukin-4, -5, and -13. These cytokines are derived from Th2 cells, from innate lymphoid cell type 2 or ILC2 cells, and from mast cells. One of the very important actions of IL-4, -5, and -13 is to attract eosinophils from the bone marrow, and then let them get into the lung tissue. So, we're going to see variable levels of eosinophils in the sputum, in the airway tissue, and in the blood of these patients. And a very large proportion, not all, but most will have an elevation of their total IgE and specific IgE to a variety of different allergens: from dust mites, to animal danders, to mold, to others.

Now again, as I mentioned earlier, non-type 2 is a much more different pathway to characterize. We know that the IL-4, -5, and -13 are not involved in this pathway, and it's been speculated perhaps that IL-17 may be a very important contributor to this pathway. Perhaps granulocyte-macrophage colony-stimulating factor (GM-CSF), as well.

These patients frequently have an underlying related bronchial infection, again, but not always. And with regard to the cellular infiltrate that we find in patients with non-type 2 asthma, typically there are no eosinophils, but rather they may have an increase in sputum neutrophils, which we define as greater than 60% of the cell types in the induced sputum.

And then, finally, these patients are not allergic. They may have a random skin test to a select pollen, but we know that in these patients, allergy does not seem to be driving the disease, and typically there is no increase in total or specific IgE.

How do we utilize these inflammatory markers, and what are we really looking for? One thing that we know is that inflammatory markers have contributed to our understanding of how to predict which patients will be more severe, and how well they'll be responsive to some of the therapies that we commonly use.



There's a number of different ways we can characterize patients using biomarkers. We can do genotyping. We can actually sample cytokines in the blood or in the airway tissue. We can look at cell populations in the airway, in the tissue, and finally in the blood. We can look at a variety of different exhaled gasses, but predominated exhaled nitric oxide. And then, finally, we can sample serum proteins, which to date have included periostin and dipeptidyl-peptidase, also known as DPP4.

I think it's useful to discuss what is an ideal biomarker? We probably haven't identified one yet, but we're in the process of trying to hone and refine our understanding of asthma to the point where we can improve upon the biomarkers that we're using.

A biomarker should be reproducible, so if you look at it in 2 points in time, you will be able to follow it adequately. It should be accurate. It should be accessible. Either a blood test or preferably something that can be obtained easily. It should correlate with the severity of the disease at baseline, and hopefully reflect the responsiveness to therapy. It should come at a reasonable cost, and ultimately be noninvasive. That's a lot to ask for. But we're going to be looking at some of the data we have with the biomarkers that we do have, starting with the eosinophil as an inflammatory biomarker.

There are variable numbers of blood and airway eosinophils present in patients with the type 2-cytokine profile, again

meaning IL-4, -5, and -13. And it's probably related to the type 2 activation due to either allergen exposure or some other driver of the inflammatory process.

Something we've learned over the past couple of years is that eosinophils in the blood and sputum can be correlated with the frequency of asthma exacerbations. The degree of airflow limitation, and finally the presence and severity of chronic rhinosinusitis with nasal polypiposis. All of the above being very important in characterizing a severe asthmatic.

When we talk about understanding how bloody eosinophils and sputum eosinophils come into play regarding the evaluation of the severe asthmatic, it's important to understand what kind of a threshold are we going to use? So, we're going to look at the parameter, either being sputum or blood eosinophils; we're going to look at different threshold values—the derived sensitivity of using that threshold, and finally the specificity.

Sputum and Blood Eosinophils Correlate With Bronchial Type-2 Cytokine mRNA

Parameter	Threshold Value	Sensitivity	Specificity
Sputum eosinophils	2%	54%	100%
	0.8%	84%	100%
Blood eosinophils	230 cells/mcl	76%	100%

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Peters SP, et al. *J Allergy Clin Immunol.* 2014;2(6):650-2.

Now, historically, we've used a level of 2% sputum eosinophils to establish that asthma has an eosinophilic phenotype. Using this approach, we have a sensitivity of picking up eosinophilic asthma, using bronchoscopy as the gold standard of only 54%, although, as you can see, the specificity's extremely high. If we drop that to the neighborhood of about 1%—and, actually, the data in this study was a little bit less than 1%. The sensitivity rises considerably without sacrificing specificity.

Very similarly, we've historically used a level of 300 to 400 eosinophils as a cutoff for identifying a type 2 inflammatory pathway.[4] But in a study that was published, again, dropping that threshold to 230 eosinophils per microliter of blood, allows you to have a much higher level of sensitivity, all the way down to 76% without at all sacrificing specificity.

Keep in mind, that when you look at papers and read the published literature, understanding the threshold and how it was derived are important. This is an example of how we can employ bloody eosinophils to get an idea of what the relative risk is for an exacerbation. Data published[5] in the last couple of years, on this slide, shows that as we look at different strata of eosinophils, starting with 100 cells, and then looking at 100 cell increments, all the way up to greater than 1000 eosinophils, we can see that the relative risks in an exacerbation rise considerably when you get into the neighborhood of 3 to 4 to 500 cells. And below that level, you don't see a large increase in the relative risk.

Blood Eosinophil Counts Correlate With Risk of Asthma Exacerbations

Claims database analysis examining eosinophil count and exacerbations requiring systemic CS or ER/hospital care

Eosinophil Stratum	Severe Exacerbations Relative Risk
201–300 cells per µL (n=25,882)	.8
301–400 cells per µL (n=15,030)	1.1
401–500 cells per µL (n=8659)	1.2
501–600 cells per µL (n=4928)	1.4
601–700 cells per µL (n=2726)	1.6
701–800 cells per µL (n=1631)	1.5
801–900 cells per µL (n=947)	1.6
901–1000 cells per µL (n=1019)	2.1
>1000 cells per µL (n=1019)	2.4

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Adapted from Price DB, et al. *Lancet Respir Med.* 2015;3:849-858.

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Sputum eosinophils have also been shown, independently, to be a very important predictor of patients who have frequent asthma exacerbations, defined as more than 2 exacerbations per year, requiring oral corticosteroids. This was a large collaborative[6] study published in Europe where they tried to characterize what features really helped identify the patients that we should be most worried about.

What we're looking at is a parameter ICS dose, oral steroid dose, the asthma control questionnaire score, and finally sputum eosinophils, and the percent that were found in their sputum induction. And we can see comparing the nonfrequent exacerbators with patients who exacerbated more than twice per year. There are some striking differences in the amount of inhaled steroid, the requirement of oral steroid, the questionnaire score that was yielded, but particularly with regard to sputum eosinophils, which was 25% plus in the patients who exacerbated frequently, but only 8.2% in the other patients. So, I think, again, this is a very accurate way, and predictive way, of identifying these patients.

Sputum Eosinophils Identify Patients With Frequent Asthma Exacerbations

Parameter	Non-frequent exacerbators	Frequent exacerbators
ICS dose (mcg/day)	800	1700*
OCS dose (mg/day)	1.7	6.7*
ACQ	1.4	2.3*
Sputum eosinophils (percent)	8.2	25.7*

*$P<0.05$

ACQ, asthma control questionnaire; ICS, inhaled corticosteroid; OCS, oral corticosteroid

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Kupczyk M, et al. *Clin Exp Allergy.* 2014;44(2):212-21.

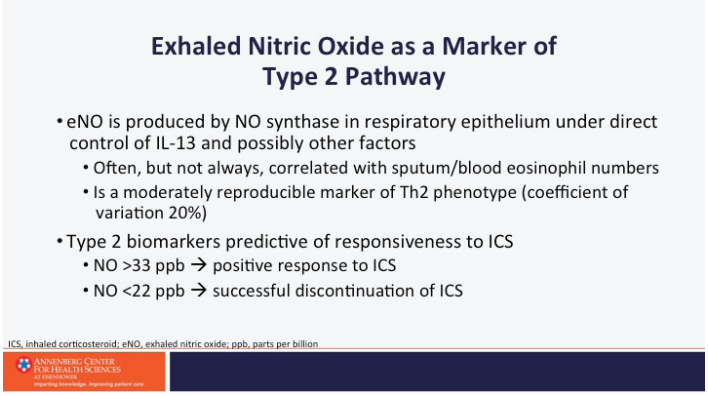
We know that not all patients have type 2 pathophysiology. And, certainly, many people have discussed and written about the role of the sputum neutrophils as an alternative inflammatory biomarker to identify the other group of patients. We're defining sputum neutrophilia as greater than 60% of the total white blood cells in the sputum of this subgroup.

Most of the time, patients with the most severe type of asthma seem to have a combination of eosinophilia plus neutrophilia, although there is a small isolated group of patients who have neutrophilia alone. But one thing you have to keep in mind when you are examining the results of this kind of test is that a number of other factors may have prominent influence over the neutrophils count in the sputum, including the recent use of inhaled corticosteroids. Things like air pollution, particularly ozone, which is a known elicitor of neutorphilic inflammation. Of course, lower respiratory-tract infections do bring neutrophils into the airway; fungi, as well. And finally, even gastroesophageal reflux [GERD] has been identified as a trigger of neutrophilia.

One thing we have to keep in mind is that this is a very nonspecific marker. But again, it's something that we can certainly take into account when trying to characterize the phenotype of a patient. Serum proteins have been very actively pursued as a marker, or biomarker, of inflammation in patients who have asthma. We know that cytokines can be examined, but it's very difficult to identify them in the blood and the sputum. Not only difficult, but also prone to inaccuracies.

If we could identify a surrogate for that cell or surrogate for the cytokine that we're trying to identify in the blood, then we've happened upon something that's much more convenient, much easier, for the practicing physician.

Some data has shown that airway interleukin-13 correlates very well with things like periostin and dipeptidyl-peptidase 4 [DPP4]. Both of these are epithelial-derived proteins that respond to the presence of interleukin-13. So, as the patient develops inflammation that's related to interleukin-13, the levels of these proteins in the serum will rise. And they've been shown to be both identifiers of this particular subtype of asthma, as well as predictive of response to agents, which do inhibit interleukin-13.



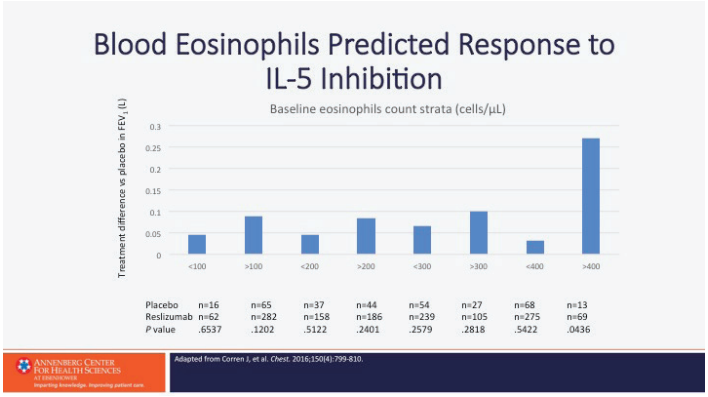
It may be that we'll never see these particular serum proteins as diagnostic tests, but something we do have, which is a very convenient test, if you happen to own the technology, is measurement of exhaled nitric oxide as a very good marker of the type 2 pathway. Now, people often believe that exhaled nitric oxide reflects eosinophilic inflammation, and in fact, there is a correlation. But we know that exhaled nitric oxide is produced by the epithelium in response to interleukin-13, very much the way that the epithelium produced periostin and DPP4.

There may be a connection between sputum and blood eosinophil numbers. It's a pretty reproducible marker of the Th2 phenotypes—somewhere in the neighborhood of about 20%. This is important so we're going to be following this over time, because reproducibility is an issue.

Something we've been able to demonstrate in a number of studies [is that] people who have a distinctly higher level of exhaled nitric oxide, around the number of 33 parts per billion, demonstrate a much stronger response to inhaled corticosteroids. And conversely, if patients have a much lower level of exhaled nitric oxide—in the neighborhood of 20 or 22—they've been able to successfully discontinue their inhaled corticosteroid dosing.

This tells us that 1 way of identifying a patient who is in fact steroid responsive or not, in fact in need of steroids, is to perform a test identifying how much nitric oxide is present.

I'm going to finish this module with a slide showing the correspondence of blood eosinophil level to the success of interleukin-5 inhibition. And the reason I'm picking this particular study is because we know that IL-5 inhibitors—anti-IL-5 drugs, like mepolizumab, reslizumab, and benralizumab, all block interleukin-5 activity from drawing eosinophils into the blood, and ultimately into the airway.



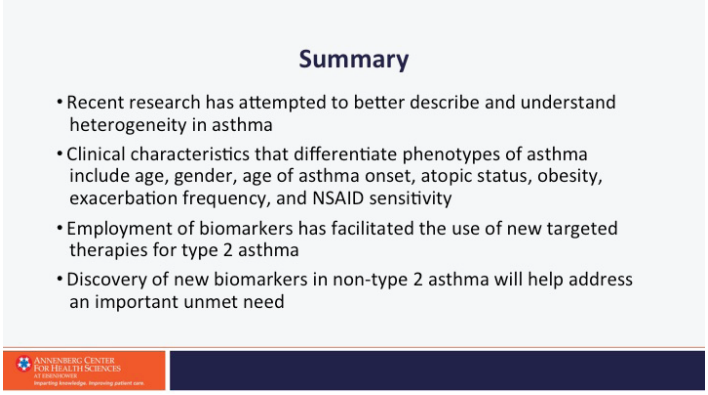
In this particular study,[7] we can look across a range of different eosinophil counts, and what we in fact find is in the lower ranges of eosinophil counts below (200, below 300, and below 400), there's no real response to the reslizumab, an IL-5 inhibitor. Finally, when we get to the level of 400 eosinophils, we see that there's a very robust amount of bronchodilatation, with improvement in FEV1, showing that, in fact, when you do inhibit IL-5 in eosinophilia, in a patient with lots of eosinophils to start with, you're going to get a

much better response than those patients who have a much lower level of this biomarker.

Let's summarize some of the things we've discussed. Number 1. There's been a lot of excellent clinical research in the past years that's really attempted to better understand this heterogeneity we've been discussing.

Number 2. There are a lot of different clinical and physiologic characteristics, along with certain inflammatory markers that we can use to distinguish asthmatics, as to which group they fall into.

Number 3. The precise use of biomarkers really helps facilitate what kind of an inflammatory the patient has going on in their particular case of asthma and allowing the physician then to determine what might be the best medication to use, whether it be an inhaled corticosteroid or whether a biologic might be indicated.



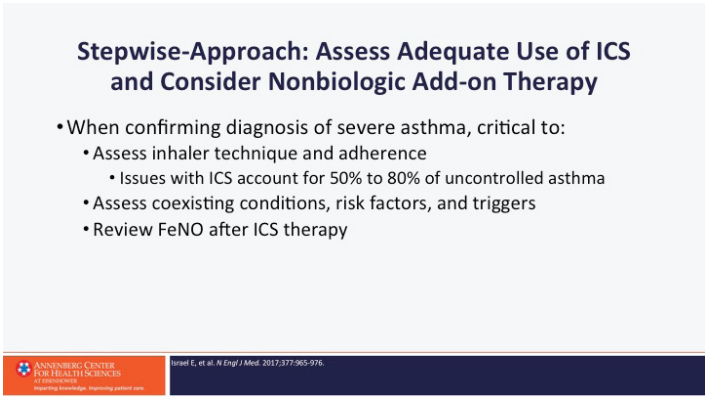
And then finally, number 4. As we discover new biomarkers and refine the use of the ones that we presently have in our armamentarium in treating this disease, I think we can expect to see not only new medications, but better outcomes with respect to severe asthma.

Novel Treatment Options

Michael Wechsler, MD

I will review the latest biologic-based targeted therapies for asthma. Discussion will differentiate between biologic agents, focusing on mechanism of action, as well as the latest safety and efficacy data of targeted therapy.

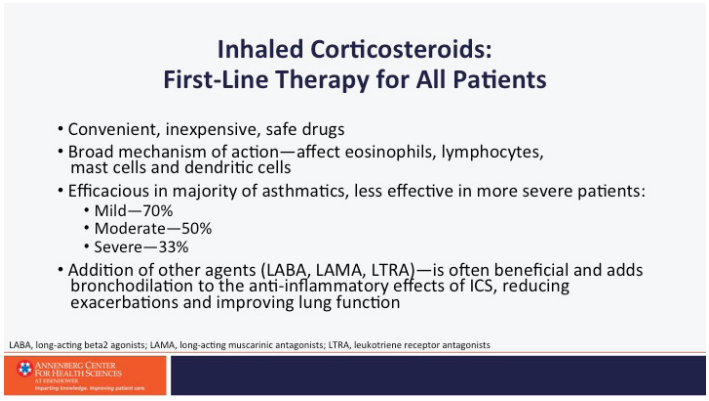
Before considering biologic therapies, it's important to take a stepwise-approach in the management of asthma. First of all, we'll need to confirm the diagnosis of asthma and also assess inhaler technique and adherence.



It's important to recognize that poor adherence to asthma medication accounts for 50% to 80% of uncontrolled asthma. Furthermore, one needs to assess coexisting conditions, risk factors, and triggers of asthma. Coexisting conditions include chronic rhinosinusitis, gastroesophageal reflux disease, obstructive sleep apnea, and other comorbidities, including vocal-cord dysfunction.

It is also important to recognize asthma triggers that can be avoided by the patient. Particularly, specific allergens that can be avoided, and potentially be causing asthma to worsen. One can also review biomarkers of asthma activity, including eosinophils, and exhaled nitric oxide, that can all be markers of adherence to inhaled corticosteroid therapy.

The first-line therapy for patients with asthma is generally inhaled corticosteroids. These therapies have been long approved for persistent asthma, from mild disease to more severe disease. Inhaled corticosteroids are convenient, inexpensive, and safe drugs that have a broad mechanism of action. They effect eosinophils, lymphocytes, mast cells, and dendritic cells, and they're effective in a majority of asthmatics. They are less effective in more severe patients, however. In those cases—in patients who are poorly controlled, despite using low doses of inhaled corticosteroids, one can increase the dose of inhaled corticosteroids, or consider addition of other agents, including long-acting beta agonists, long-acting muscarinic agents, or leukotriene receptor antagonists.



These therapies are often beneficial and add bronchodilation to the anti-inflammatory effects of inhaled steroids. They all help in terms of reducing exacerbations, improving lung function, and improving symptoms related to asthma.

When considering inhaled corticosteroids add-on therapy, it's important to recognize that inhaled corticosteroids—particularly inhaled corticosteroids, but also oral corticosteroids, with or without other controller therapies—

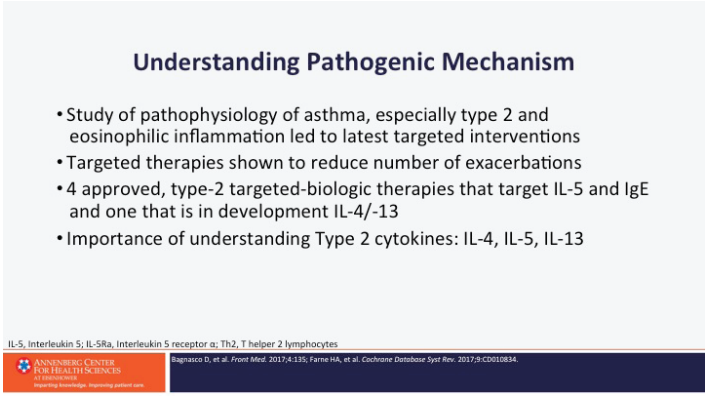
may offer only partial control of severe asthma. For those patients who are on either inhaled corticosteroids, monotherapy, or a combination of therapies, one should consider, first, nonbiologic add-ons, and then consider treatments with biologic agents.

The nonbiologic add-ons to consider include long-acting beta agonists, which improve dilation of airways through activation of beta-agonist receptors; tiotropium, which is a long-acting muscarinic agent; macrolide antibiotics have been tested, [but]not approved for asthma, but have been shown to improve outcomes in patients with asthma; leukotriene modifiers and bronchial thermoplasty. All of these therapies have been shown to improve outcomes in patients with asthma.

If these therapies are tried, then afterwards, if they're not successful, one should asses for targeted treatments with biologic agents. This may include workup with specific biomarkers.

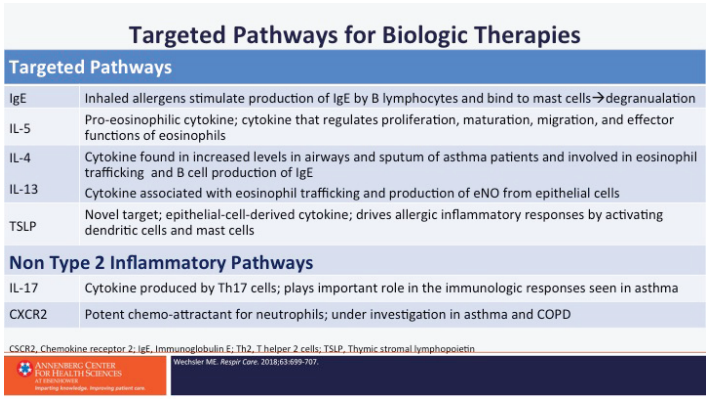
When treating patients with inhaled corticosteroids, the next approach in those who are poorly controlled is often to increase the inhaled corticosteroids. For patients who are on combinations of therapy, many doctors still give oral corticosteroids, such as prednisone; however, with regard to inhaled corticosteroids, there's a limited dose-response curve. For oral corticosteroids, there are many side effects. Corticosteroids are often associated with systemic toxicity, including adrenal insufficiency, weight gain, hypertension, cataracts, glaucoma, and osteoporosis. So, in those patients, it's really important to consider patients for more targeted therapies.

To better understand novel asthma treatments, one needs to understand the underlying asthma pathophysiology. Our recent studies have demonstrated a significantly improved understanding of the underlying pathophysiology of asthma, especially type 2 asthma and eosinophilic inflammation, that have led to the latest targeted interventions.



These targeted therapies have been shown to reduce the number of exacerbations of asthma, improve lung function, and improve asthma-related symptoms. Currently, we have 4 approved targeted therapies in asthma, including those therapies that target interleukin-5 and IgE, and 1 therapy that's in development, that targets interleukin-4 and -13. [Note: the FDA approved asthma indication for dupilumab on October 19, 2018.] It's important to understand all of these type 2 cytokines, including IL-4, IL-5, and IL-13, as well as the role that IgE plays in the pathophysiology of asthma.

Asthma can broadly be broken down into type 2 inflammation and non-type 2 inflammation. Type 2 inflammation is brought on by activation of both Th2 cells, as well as innate lymphoid cells, or ILC2 cells. These cells bring about and produce type 2 cytokines, including IL-4, IL-5, and IL-13. IL-4 is involved in activation of B-cells that produces IgE. And IgE binds to mast cells and causes mast-cell degranulation, and release of a variety of different mediators, including histamine.



IL-5 is a pro-eosiniphilic cytokine that regulates proliferation, maturation, migration, and effector function of eosinophils. IL-13 is a cytokine that's associated with eosinophil trafficking, and production of nitric oxide from epithelial cells, as well as mucus production. IL-4 is a cytokine that's found in increased levels in the airways and sputum of asthma patients, and is involved in eosinophil trafficking, and in B-cell production of IgE.

TSLP is a novel target. It's short for thymic stromal lymphopoietin, and it's an epithelial cell-derived cytokine that drives allergic inflammatory responses, and drives type 2 inflammatory responses, by activating dendritic cells and mast cells.

In addition to type 2 pathways of inflammation that are generally brought on by allergens, there's also non-type 2 inflammatory pathways, that are generally brought on by bacteria, fungus, viruses, and irritants, including smoking. The key to non-type 2 inflammation is IL-17. IL-17 is a cytokine that's produced by Th17 cells and plays and important role in immunologic responses seen in asthma. Also, important in non-type 2 inflammation is interleukin-6, interleukin-8, and TNF-a, as well as CXCR2, that's a potent chemoattractant for neutrophils, and that's currently under investigation in asthma and COPD.

Other non-type 2 cytokines that are important, include interleukin-33, which also plays a role in activation of both type 2, as well as non-type 2, inflammatory pathways.

Currently, we have several biologics that are approved for management of asthma. These include agents that target interleukin-5, IgE, and therapies that are in development, including those therapies that target the IL-4 receptor that blocks both IL-4 and IL-13. Let's talk about each of these.

Approved Biologics and Targets

Target Antigen	Agent (FDA Approved)	Mode of Delivery	Safety and Adverse Events	Clinical Data	Trial Results
IL-5Rα	Benralizumab (Nov 2017)	Injectable	Safe and well tolerated. Most common AEs: nasopharyngitis; asthma worsening (CALIMA: 14% Q4W group, 11% Q8W, 15% placebo arm) (SIORCCO: 13% vs 19% of placebo-treated)	**Approved** for use in eosinophilic asthma. For patients with blood eosinophil count of at least 150/mL.	**CALIMA trial** (n=1306): Q4W & Q8W regimens decreased exacerbations by 36% and 28%, respectively; lowered blood counts[1] **SIROCCO trial** (n=1,205): 48 weeks 1 of 3 add-on SQ; exacerbations reduced 45% & 51% in Q4W and Q8W; Exacerbations decreased 17%–30% in patients with <300 blood eosinophils/μL[2]
IL-5	Reslizumab (April 2017)	Intravenous (3 mg/kg) monthly	Safe and well tolerated in patients exposed >2 yr [3] Infusion-site reactions uncommon (<2%). Most common AEs: nasopharyngitis, upper respiratory tract infections, sinusitis, influenza, and headache. SAEs more frequent in placebo grp. No helminthic infestations reported. 2 in reslizumab grp anaphylactic reactions, but negative for ADAs. Further research needed in special population.	**Approved** for maintenance treatment w/severe exacerbations, despite on current asthma medications. For patients with blood eosinophil count of at least 400/mL.	**BREATH program:** 4 studies (n=1656), serum eosinophil counts reduced (mean diff vs placebo: −476.83, 95% CI −499.32 to −454.34)[3] Reduced number of eosinophils in the blood and lungs; decreased blood eosinophils.[3]

Asthma Control Questionnaire 5 (ACQ5); LABA, long-acting β-agonists; LD, loading dose; mL, microliter; SQ, subcutaneous; QoL, quality of life

1. Fitzgerald JM, et al; *Lancet*. 2016;388:2128–2141. 2.Bleecker ER, et al. *Lancet*. 2016;388:2115–2127. 3. Cazzola M, et al. *Expert Opin Drug Saf*. 2018;17:429-435.

Benralizumab is a monoclonal antibody that was approved for the management of eosinophilic asthma in November of 2017. It binds to the IL-5 receptor alpha, as an injectable therapy that's safe and well tolerated. The SIROCCO[8] and CALIMA[9] studies demonstrated that benralizumab offers significant benefits in terms of reduction in asthma exacerbations in patients with eosinophilic asthma, who are poorly controlled on inhaled steroids and long-acting beta agonists. After being administered every 4 weeks for the first 3 doses, it can then be administered every 8 weeks, thereafter, and has been shown to be effective in that patient population. In a steroid-sparing study, published by Param Nair and colleagues in *New England Journal of Medicine* in 2017,[10] benralizumab was shown to reduce asthma exacerbations by approximately 70%, and reduce steroid dosing, also by about 50%, compared to placebo.

Another monoclonal antibody that targets IL-5, not the IL-5 receptor, is reslizumab. Reslizumab was approved in April of 2016 for management of patients with eosinophilic asthma. It's an intravenous therapy that's dosed 3 mg per kg and has been shown to be effective both in terms of exacerbation reduction, but also in terms of improvement in lung function in patients with severe asthma. The greatest results were seen in patients who had blood eosinophil counts above 400. And it's been shown in several studies now, to improve not just exacerbations but also symptoms and asthma-related quality of life. Of course, it's also been shown to reduce the number of eosinophils in the blood, as well as in the sputum.

Mepolizumab is another monoclonal antibody that was the first monoclonal antibody that targeted interleukin-5. It's been shown to improve asthma exacerbations in patients

Approved Biologics and Targets *(continued)*

Target Antigen	Agent (FDA approved)	Mode of Delivery	Safety and Adverse Events	Clinical Data	Trial Results
IL-5	Mepolizumab (Nov 2015)	Injectable	Safe and well tolerated Most common AEs and SAEs: injection-site reactions (12%), infections (7%), systemic reactions (3%), serious cardiac, vascular, thromb events (3%); malignancies (2%), serious ischemic events (<1%)	First long-term safety data reported for IL-5; **Approved** for patients with blood eosinophil count of at least 150/mL.	**COLUMBA trial** (n=347): Pts treated w/100 mg SQ every 3-4 wks for 3.5–4.5 yrs; 61% decrease in exacerbation rate, 78% reduction in blood eosinophils by wk 4, sustained; 1/3 experienced no exacerbations; ACQ5 improved.[1] Dream study: reduced exacerbations by 40-60%; 50% reduction in CS. Blood eosinophil counts decline by 75% within a month, failure to achieve decrease raises questions about biologic efficacy in patient; FeNO minimally reduced.[2,3]
anti-IgE Ab	Omalizumab (2003)	Injectable	AEs (80.4% vs 79.5%) and SAEs (9.3% vs 10.5%) were similar in the omalizumab and placebo groups, respectively. Note concerns about anaphylaxis and cardiovascular risk and lack of efficacy in some patients	**Approved** for patients with total serum IgE level >30 IU/mL; for moderate-to-severe persistent allergic asthma whose asthma symptoms are not controlled by ICS. **MoA:** Binds to free IgE; prevents IgE from binding to high-affinity receptors	**Hanania et al.** (n=850): 48 wks decreased exacerbations 25%; improved asthma QoL scores. Overall trial history: reduced asthma exacerbations, serum-free IgE, ICS dose; QOL improved.[4]
Anti-IL-4/-13	Dupilumab (FDA approved for asthma indication October 19, 2018.)	Injectable	Safe and well tolerated. AEs similar across groups: injection-site reactions (17% vs 8% placebo, respectively), back pain (4%, both groups), eosinophilia (4% vs 1%, respectively).	**Approved** for patients with asthma previously treated with medium-dose or high-dose ICS and LABAs. Consider for patients with allergies , elevated IgE, eosinophilia, or high eNO levels.	**Quest trial** (n=1902); 4 grps 200 mg (400 mg LD) and 300 mg (600 mg LD) every other week; 60–80% reduction in exacerbations; Reduced FeNO and IgE levels;, Improved lung function and reduced dependence on OCS.[5,6]

1. Ortega H, et al. Presented at ATS 2018. Abstract A1367; 2. Bel EH, et al. *N Engl J Med*. 2014;371:1189-97; 3. Pavord ID, et al. *Lancet*. 2012; 380:651-9; 4.Hanania NA, et al. *Ann Intern Med*. 2011;154:573-82; 5. Castro M, et al. *N Engl J Med*. 2018;378:2486-2496; 6. Wenzel S, et al. *Lancet*. 2016;388.31-44.

with eosinophilic asthma and has been shown to not only reduce exacerbations, but one study also demonstrated significant reduction in steroid dosing, and in exacerbations in patients who were treated with oral corticosteroids. It's dosed on a monthly basis, subcutaneously, 100 mg each month. It's also been approved by the FDA at a higher dose, 300 mg, for another eosinophilic condition, eosinophilic granulomatosis with polyangiitis.

Omalizumab was the first monoclonal antibody approved for the management of asthma. It was approved in 2003 as an injectable, subcutaneously administered monoclonal antibody that targets IgE, immunoglobulin E. IgE generally binds to mast cells, and when it interacts with an allergen, and cross links with other IgEs, results in mast-cell degranulation and release of different mediators, including leukotrienes and histamines.

Early data demonstrated that omalizumab is very effective in patients with allergic asthma. It's also approved for patients with urticaria. It's been shown to reduce asthma exacerbations on the order of about 50% in patients with the allergic asthma phenotype.

However, recent studies by Nick Hanania and colleagues[11] have also demonstrated that omalizumab is effective, particularly in patients with high eosinophils, high IgE, high periostin, and high nitric oxide levels, offering greater benefit than in patients that have lower levels of those biomarkers.

The newest monoclonal antibody that's been in development is a monoclonal antibody that targets the interleukin-4Ra receptor alpha. The IL-4Ra binds to both IL-4 (interleukin-4), as well as interleukin-13—2 important cytokines important in both eosinophil trafficking, production of mucous, as well as production of nitric oxide.

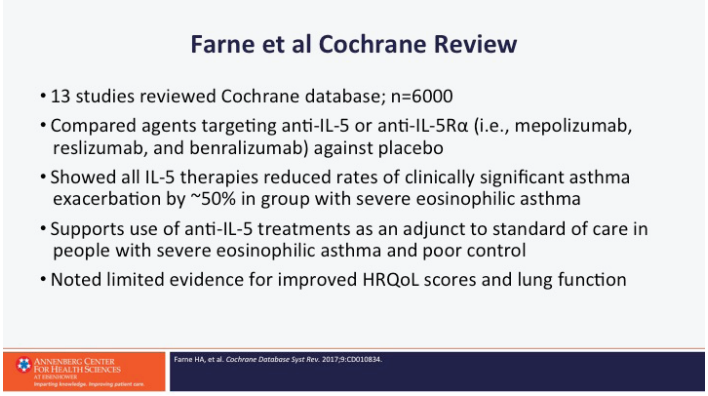
Dupilumab is currently under FDA review with a target action date of October 2018. [The FDA approved asthma indication for dupilumab on October 19, 2018.] It's been shown to be safe and well tolerated.[12] Phase 3 studies, as well as phase 2 studies, have demonstrated broad efficacy with significant reduction in asthma exacerbations in patients with eosinophilic asthma, patients with high nitric oxide levels, and patients who are on or not on oral corticosteroids.

The magnitude of benefit with dupilumab has been demonstrated with reduction in exacerbations, particularly in patients with high EOs and high ENO. Also, it's been shown to be effective in patients who are on oral corticosteroids. In that patient population, as well as demonstrated by a publication by Klaus Rabe and colleagues,[13] dupilumab has been shown to reduce exacerbations, as well as improve lung function, and allow or facilitate corticosteroid withdrawal.

One of the challenges that clinicians currently face, is deciding between different biologic agents. One of the problems is that there are no head-to-head studies comparing one biologic to another.

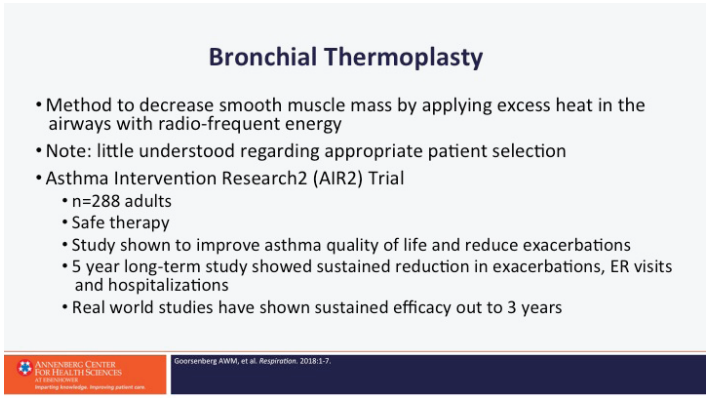
However, in 2017, there was a Cochrane review[14] that evaluated 13 studies, that included 6,000 patients who

received different biologic therapies. This Cochrane review compared agents targeting the IL-5 or IL-5 receptor against placebo, and evaluated mepolizumab, resolizumab, and benralizumab. The Cochrane review showed that all IL-5 therapies reduced rates of clinically significant asthma exacerbations by about 50% in patients who had severe eosinophilic asthma and supported the use of anti-IL-5 therapies as an adjunct to standard of care in people with severe eosinophilic asthma, and poor control. It's important to recognize however, that there was limited evidence for improved health care-related quality of life, as scores, as well as lung function.



Another therapy that's important to consider for patients with severe asthma is bronchial thermoplasty. Bronchial thermoplasty is a procedure that involves delivering heat to the airways of patients with severe asthma. This is done bronchoscopically, with a catheter that's deployed through a bronchoscope into the airways. At one end of the catheter, there is a basket that heats up, and at the other end of the catheter, the catheter is hooked up to a heat source, that delivers thermal energy, up to 65°C.

Bronchial thermoplasty has been approved by the FDA in 2011, and is demonstrated to reduce asthma exacerbations. Five-year long-term studies have shown sustained



reduction in exacerbations, emergency room visits, and hospitalizations. It's been shown to be a safe therapy with no evidence of any long-term reduction in lung function; no evidence of bronchiectasis. Recently, some real-world studies have demonstrated sustained efficacy out to 3 years in a nonclinical-trial situation in patients who receive this procedure. This is another viable option for patients with severe asthma.

In conclusion, asthma therapy has evolved a long way from just use of inhalers in patients with moderate-to-severe asthma. We now have more targeted therapies, that target-specific pathways. We've recognized the importance of evaluating for endotypes of asthma—the specific mechanisms of asthma in a given individual—to identify whether a patient has type 2 inflammation, or non-type 2 inflammation, eosinophilic asthma, or non-eosinophilic asthma, IgE-mediated asthma or non-IgE-mediated asthma. Identifying these specific targets allows us, by using biomarkers, to identify appropriate therapies that are novel, targeted for the patient, so that we can identify the right drug for the right patient at the right time, based on the science of the disease.

This is an exciting time for the management of asthma as we have new therapies now. It is exciting because we will soon be developing other new therapies that are on the horizon.

Treatment Strategies Discussion

Jonathan Corren, MD, & Michael Wechsler, MD

Dr. Corren and Dr. Wechsler review selected biologic-based therapies given to patients with severe asthma based upon their select phenotype and endotype. They also discuss optimal treatment regimens based upon asthma severity and comorbid conditions.

Jonathan Corren, MD: What are the strategies that we can use to maximize standard therapies for patients with asthma?

Michael Wechsler, MD: In terms of maximizing standard medical therapies, it's important to recognize the importance of the environment as well as adherence and comorbidities, and then to recognize that we have novel therapies that can address our unmet needs.

First of all, it's important to recognize the role of the environment. Allergen avoidance is really key in terms of identifying strategies that can help our patients with asthma. Patients who are allergic to cats should avoid cats. Patients who have occupational allergies should try to avoid those or

mitigate those to some extent to prevent deleterious effects on their asthma.

Management of comorbidities is also really important. Addressing chronic rhinosinusitis, gastroesophageal reflux disease, vocal-cord dysfunction, sleep apnea—all can help address issues associated with asthma. In addition to avoiding environmental allergens, allergy immunotherapy, or allergy shots, have been shown to be quite effective in terms of ameliorating asthma symptoms.

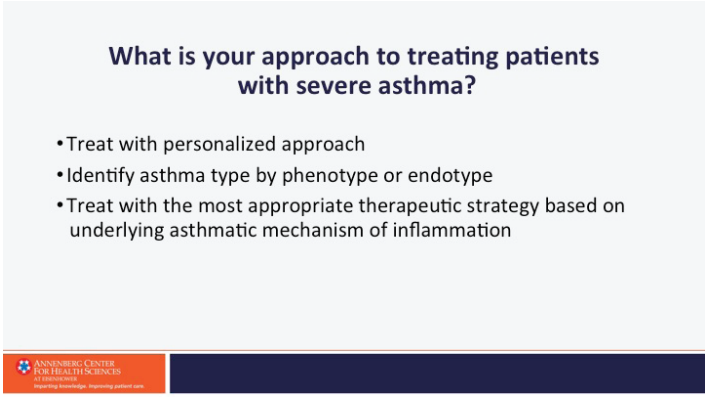
As well, we now have the availability of a variety of different biologic therapies for the management of asthma. Anti-IL-5 therapies, including benralizumab, mepolizumab, and reslizumab have all been shown to be effective in patients with eosinophilic asthma.

Anti-IgE therapy, including omalizumab, has been shown to be effective in patients with allergic asthma. And, on the horizon is anti-IL-4 receptor alpha therapy, including dupilumab, which has been shown to improve lung function and reduce asthma exacerbations in patients with type-2 asthma, including both allergic asthma as well as eosinophilic asthma.

In addition to all of these therapies, we also have available to us bronchial thermoplasty. Bronchial thermoplasty is an effective treatment strategy for patients who have severe asthma, as it's been shown to reduce asthma exacerbations, emergency room visits, and hospitalizations. It's a therapy that involves delivering thermal energy, or heat, to the airway walls using a catheter delivered bronchoscopically. The catheter heats up the airway wall and reduces airway smooth muscle, and improves asthma exacerbations.

Jonathan Corren, MD: What is your approach to treating patients with severe asthma?

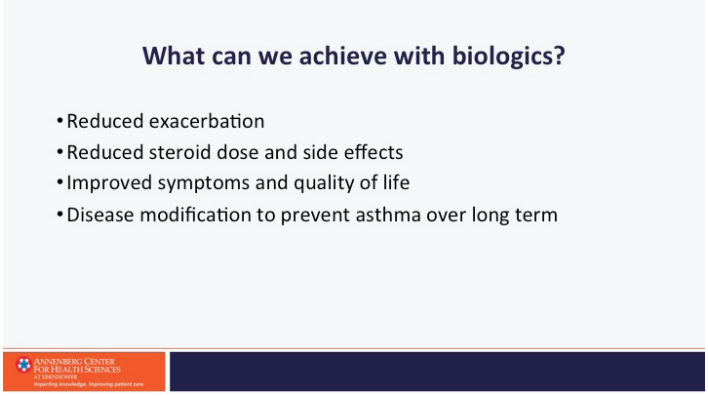
Michael Wechsler, MD: My general approach is to treat patients with the most appropriate therapeutic strategy—to identify a personalized approach, so we can give the right drug to the right patient at the right time. To do this, I try to identify the type of asthma that the patient has, and you can do this by looking at both phenotypes or endotypes. The goal is to try to treat based on an underlying asthma mechanism of inflammation. So, my strategy generally involves identifying patients based on whether or not they've got type-2 inflammation or non-type 2 inflammation, and then identifying whether they have elevations in eosinophils, nitric oxide, or IgE.



I also use surrogate measures of asthma endotypes that look at particular phenotypes. So, patients who've got allergies often have IgE-mediated disease. Many patients that have chronic rhinosinusitis often have IL-5 or IL-4-mediated disease. And patients who've got atopic dermatitis also often have IL-4-mediated disease. The goal is to try to use the most appropriate therapeutic strategy in the right patient at the right time.

Michael Wechsler, MD: So, what can we achieve with biologics?

Jonathan Corren, MD: Over the past 8 to 10 years, we've seen a number of different outcome measures improve markedly with carefully and appropriately chosen biologic medication. Because these drugs are expensive, and they require an injection in the office, we want to choose wisely. We want to choose patients who are in the greatest need of this kind of a drug. This would imply, typically, that a patient has multiple exacerbations, 3 or typically at least 2 or more, that required a course of oral corticosteroid to bring the disease under control.



And what we have seen with biologic medications—whether it be omalizumab, or the anti-IL-5 drugs, or dupilumab—is that they do reduce exacerbations significantly.

With some, but not all of these drugs, there's been marked reductions in oral corticosteroid requirements. And what comes to mind are the drugs mepolizumab, benralizumab, and dupilumab, have all published data indicating that there is significant reduction in oral-steroid requirements, while at the same time a much better improvement in overall disease control, with fewer exacerbations.

We shouldn't just think of exacerbations, however, although they are very important. But we should consider the daily burden of disease and quality of life that's impaired by having asthma. And in this situation, what we can expect to see is less asthma symptoms, better quality of life. And with better quality of life, the things people want to do: better sleep, better exercise, and better ability to stay and work effectively at their job.

And then finally something we look forward to—and at this point in time we can't say that we have achieved it, although

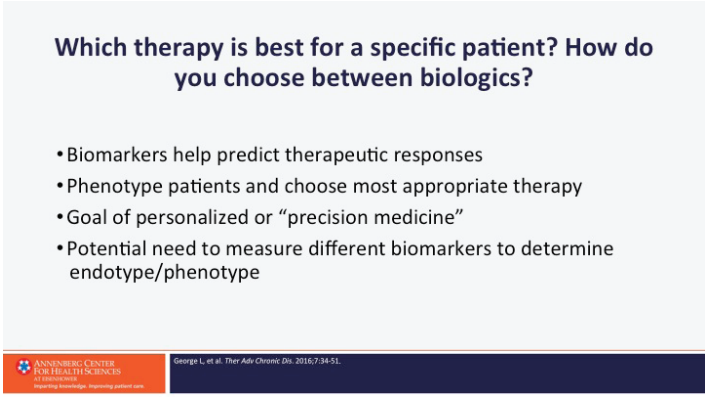
long-term studies with new biologics may bear this out—is a reduction in long-term airway remodeling. This is actual disease modification or maybe even disease remission. And now with drugs such as the IL-5 antagonists, as well as IL-4 receptor antagonist, we may in fact achieve that.

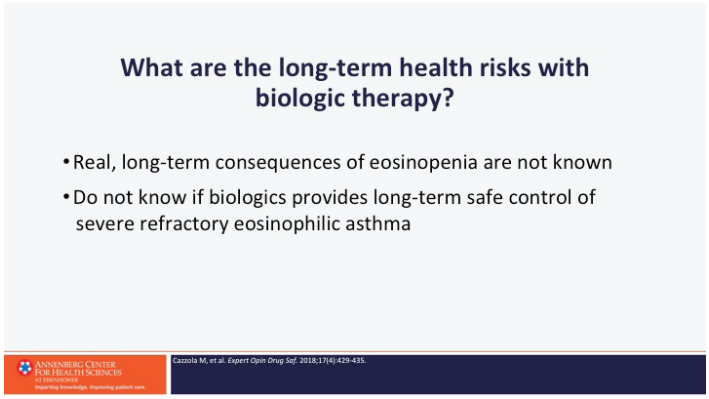
Jonathan Corren, MD: I have a couple of questions. First, which therapy is best for a specific patient? And then secondly, how do you choose between biologics?

Michael Wechsler, MD: I generally use biomarkers to help predict therapeutic responses. Biomarkers, like eosinophils in the blood or in the sputum, nitric oxide, IgE levels, for instance, are all useful biomarkers. We clearly need other biomarkers and other biomarkers are in development. Biomarkers, like periostin and DPP-4 or dipeptidyl peptidase-4, are also in development that may help us decide which strategies are useful for which patients.

In general, I try to phenotype patients and choose the most appropriate therapy. So, if someone has predominantly allergic asthma, I'll use anti-IgE. If someone has predominantly eosinophilic asthma, I could use either anti-IL-5 or an anti-IL-4/13 therapy, if it's available. If someone's got an elevation in nitric oxide level, an anti-IL-4/13 strategy is probably the most appropriate therapy for that patient.

Our goal is to provide a personalized, precision medicine approach. And our goal is to try to identify biomarkers that can *predict* specific endotypes in a given individual. In addition, I sometimes use phenotypes to help me decide which endotype is most likely to occur. So, if someone has concomitant atopic dermatitis, I'm more likely to use a drug like dupilumab, which targets IL-4/13.





Michael Wechsler, MD: What are the long-term health risks with biologic therapy?

Jonathan Corren, MD: One of the ways of answering this question is to examine a biologic medication that we've had available to us for the past 15 years, and that is omalizumab. There have been some excellent long-term, open-label studies of this drug. And what we've been able to glean from these studies is the drug appears extremely safe. The other biologics we have available to us, particularly the anti-IL-5 drugs and the anti-IL-5 receptor drug (mepolizumab, reslizumab, and benralizumab), there have been 1-year follow-up studies, and with mepolizumab, an even longer period of observation. And thus far, today, we have not found any long-term health risks of using these drugs for prolonged periods of time.

It may be in the future that something will become discovered, but at least at this point in time, I think we can rest assured that these are safe medications with adverse events very comparable to placebo.

On the Horizon

Michael Wechsler, MD

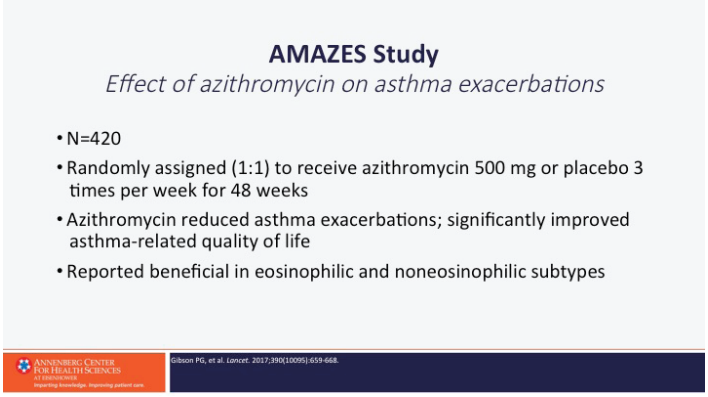
I will be discussing specific therapies in development for asthma, and we'll also address persistent questions in the treatment of severe asthma, such as long-term treatment with biologics, and the potential for combination therapy.

One of the most interesting developments in the management of severe asthma has been the consideration of use of antibiotics in the management of patients with severe asthma. Antibiotics that are effective against atypical bacteria may have anti-inflammatory activity. And several studies have been done showing the use of macrolide antibiotics, such as azithromycin, or ketolide antibiotics, such as telithromycin, may have benefits in patients with severe asthma.

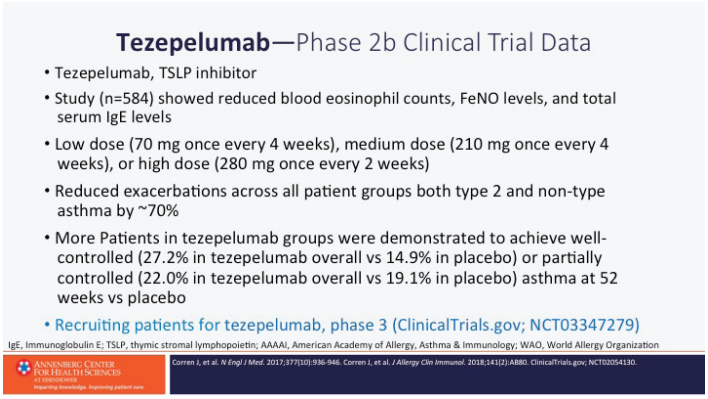
In one of the most recent studies, the AMAZES study,[15] published by Gibson and colleagues in 2017, demonstrated a beneficial effect of azithromycin on asthma exacerbations. In a study that enrolled 420 subjects, individuals were randomly assigned to receive azithromycin, 500 mg, 3 times a week, vs placebo, for 48 weeks.

In this study, azithromycin reduced asthma exacerbations and significantly improved asthma-related quality of life. The reduction in exacerbations was on the order of about 40%, similar to many of the biologics that have been studied. Not only that, but there was reported benefit in both eosinophilic, as well as, non-eosinophilic subtypes of asthma. And thus, many patients are being evaluated for consideration of use

of a macrolide antibiotic, such as azithromycin in patients with severe asthma.



Also, on the horizon is an important therapy that targets TSLP, thymic stromal lymphopoietin. Tezepelumab is currently in phase 3 studies—they are currently in recruitment—but a phase 2b study that was published in 2017 by Jonathan Corren in the *New England Journal of Medicine*[16] showed that tezepelumab was effective in terms of reducing asthma exacerbations across all patient groups, both type 2 asthma, as well as non-type 2 asthma. And the reduction [in] exacerbations was seen at a range of approximately 70%. This therapy, administered subcutaneously, 70 mg, every 4 weeks, with dosing up to 280 mg every 2 weeks, demonstrated that patients who received tezepelumab had benefits across a variety of outcomes. In particular, more patients in tezepelumab groups were demonstrated to achieve well-controlled, or at least partially controlled, asthma at 52 weeks versus placebo. It's exciting to see what will happen with tezepelumab as phase 3 studies are completed.



It's exciting that there are several other emerging target-specific therapies. One of the most exciting and newest therapies in development are CRTh2 antagonists that block the prostaglandin D2 receptor. One of the therapies in the CRTh2 categories that's furthest along in development is fevipiprant. This has showed promising results in cellular, functional, and clinical outcome studies has been demonstrated to have acceptable safety. It's been showed to decrease prostaglandin D2-mediated eosinophil migration. And, in patients with eosinophilic asthma, it's been showed to improve lung function and symptoms.

One of the most exciting components of fevipiprant, is that it's an oral therapy. And, so may be considered to [be] used prior to some other biologic agents. It's currently in phase 3 development, and it will be interesting to see what emerges from those data.

The biggest unmet need in asthma, is probably, however, therapies that target non-type 2 inflammation. We already have therapies that target type 2 inflammation, including those that bind IL-5, IL-4 receptor, and IgE. So, what we need are therapies that target non-type 2 inflammation.

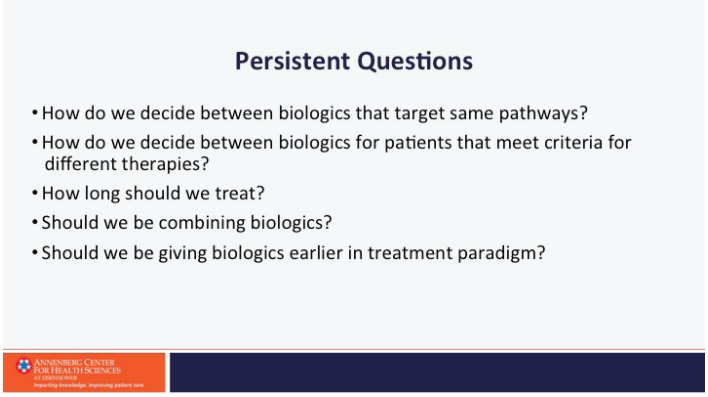
Currently in development [are] CXCR2 antagonists that decrease IL-8 levels. These have shown promise in early trials. Navarixin reduced sputum and blood neutrophils, and there was a trend towards better asthma control based on asthma control questionnaire, but there was no significant change in lung function.

Another potential target are IL-6 antagonists.[17] Interleukin-6 is a potential biomarker of systemic inflammation. And, along with C-reactive protein (CRP), may be a biomarker of non-type 2-mediated severe asthma, particularly in patients who have obesity-associated asthma. There are currently interleukin-6 therapies that are available for other indications, but studies are needed and are initiating in patients with severe non-type 2 asthma.

Another important therapy that's in development for non-type 2 asthma is interleukin-17 antagonists. Brodalumab is one therapy that was evaluated. It didn't achieve significant clinical benefits, but perhaps not the right patients were selected in a limited study published by Busse and colleagues.[18]

Other therapies that target asthma pathways a bit more proximally, include therapies that target interleukin-33 and interleukin-25, so-called alarmins, that along with TSLP, activate a broad range of cells and a broad range of cytokines. These therapies are both currently in development in phase 2 and are exciting and may show significant promise in the future.

While it's exciting to have newly available therapies that target specific pathways for severe asthma, many questions persist regarding their use. In particular, how do we decide between biologics that target the same pathway? How do we decide between mepolizumab, reslizumab, and benralizumab? Is it based on dosing strategy? Is it based



on patient preference? Or, are there specific biomarkers that can help us decide between one therapy vs another?

Furthermore, how do we decide between biologics for patients that meet criteria for different therapies? How do we decide between anti-IL-5 therapies, anti-IgE therapies, and anti-IL-4 antagonists?

All of these therapies compete in a type 2 anti-inflammatory space. And how do we decide which drug is best for which patient? Should we be combining biologics for these patients? Perhaps some patients have both IL-5-mediated inflammation and IL-4-mediated inflammation and may benefit from blockade of both these 2 different cytokines. Perhaps patients have both IL-4-mediated inflammation and IgE-mediated inflammation and may benefit from each of those different types of treatment strategies.

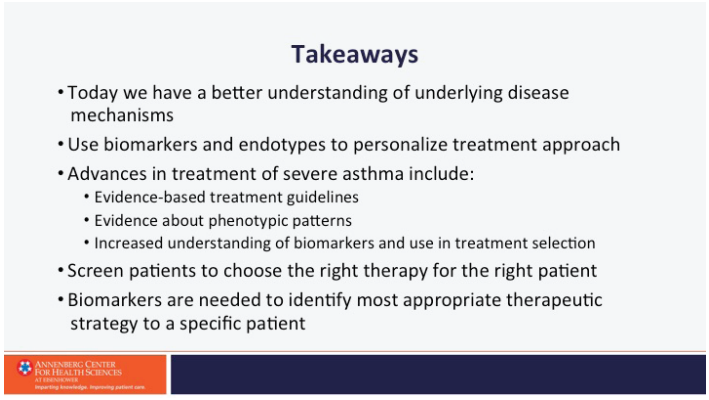
Another question that emerges, is how long should we treat our patients with these biologics? Six months, 12 months, forever? We don't have answers to many of these questions, but we need to do further research to address some of these issues. We need to do head-to-head studies. And we need to do studies in which we treat patients who are doing well with these therapies, and randomize them to continue therapy, or stop therapy, to decide how long we should treat them.

Another question that emerges is shouldn't we be giving biologics earlier in the treatment paradigm? Is it important to perhaps give these biologics to address the underlying asthma pathophysiology, and overall asthma treatment course. Can we affect long-term asthma development by, either giving these drugs earlier on with patients with milder asthma, or at younger ages to infants and children who may be at risk for developing asthma down the road?

Clearly, a lot of research is needed. We need to determine the optimal duration of biologic treatment. We need to evaluate long-term safety effects of treatment with biologics. We need to evaluate the risk of relapse on withdrawal of these therapies. And, we need more research on biomarkers to assess treatment response, identification of neurobiologics, and to help us decide which drug is right for which patient.

We also need to develop newer therapies for patients with non-type 2 asthma and non-eosinophilic asthma. That, I would say, is probably the biggest unmet need, because there are no therapies right now for those patients.

Today, we have a better understanding of underlying disease mechanisms of asthma, and we've recognized the importance of using biomarkers and endotypes to personalize our treatment approach for patients with severe asthma.



We've made many advances in the treatment of severe asthma, and this has resulted in evidence-based treatment guidelines. And, we now have evidence about specific phenotypic patterns that track with different endotypes. We also have an increased understanding of biomarkers and their use in treatment selection.

We now have the capacity to screen patients to choose the right therapy for the right patient at the right time. Clearly, biomarkers are needed to identify the most appropriate therapeutic strategy for a specific patient, and new biomarkers are needed.

It's [an] exciting time for the management of patients with severe asthma. We have new therapies; we're understanding our disease better; and hopefully, we'll be able to have a huge impact on the management of patients with severe asthma down the road for both type 2 asthma, as well as non-type 2 asthma.

References

1. Spector SL, Farr RS. The heterogeneity of asthmatic patients—an individualized approach to diagnosis and treatment. *J Allergy Clin Immunol*. 1976;57(5):499-511.
2. http://www.severeasthma.org
3. Moore WC, Meyers DA, Wenzel SE, et al. and for the National Heart, Lung, and Blood Institute's Severe Asthma Research Program. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med*. 2010; 181(4): 315–323. doi:10.1164/rccm.200906-0896OC
4. Peters SP. Asthma phenotypes: nonallergic (intrinsic) asthma. *J Allergy Clin Immunol Pract*. 2014;2(6):650-2. doi:10.1016/j.jaip.2014.09.006
5. Price DB, Rigazio A, Campbell JD, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med*. 2015;3(11):849-58. doi:10.1016/S2213-2600(15)00367-7
6. Kupczyk M, ten Brinke A, Sterk PJ, et al. Frequent exacerbators—a distinct phenotype of severe asthma. *Clin Exp Allergy*. 2014;44(2):212-21. doi:10.1111/cea.12179
7. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: Effects across a broad range of eosinophil counts. *Chest*. 2016;150(4):799-810. doi:10.1016/j.chest.2016.03.018.
8. Bleecker ER, Fitzgerald JM, Chanez P, et al; SIROCCO study investigators. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (SIROCCO): a randomized, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115–2127.
9. Fitzgerald JM, Bleecker ER, Nair P, et al; CALIMA study investigators. Benralizumab, an anti-interleukin-5 receptor monoclonal antibody, as add-on treatment for patients with severe, uncontrolled eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2128–2141.
10. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448-2458. doi:10.1056/NEJMoa1703501
11. Hanania NA, Alpan O, Hamilos DL, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med*. 2011;154:573-82.
12. Wenzel S, Castro M, Corren J, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting β2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet*. 2016;388:31-44.
13. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475-2485. doi:10.1056/NEJMoa1804093
14. Farne HA, Wilson A, Powell C, Bax L, Milan SJ. Anti-IL5 therapies for asthma. *Cochrane Database of Syst Rev*. 2017; 9:CD010834. doi:10.1002/14651858.CD010834.pub3
15. Gibson PG, Yang IA, Upham JW, et al. Effect of azithromycin on asthma exacerbations and quality of life in adults with persistent uncontrolled asthma (AMAZES): a randomised, double-blind, placebo-controlled trial. *Lancet*. 2017;390(10095):659-668. doi:10.1016/S0140-6736(17)31281-3.
16. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936-946. doi:10.1056/NEJMoa1704064
17. Naik SP, Mahesh PA, Jayaraj BS, Madhunapantula SV, Jahromi SR, Yadav MK. Evaluation of inflammatory markers interleukin-6 (IL-6) and matrix metalloproteinase-9 (MMP-9) in asthma. *J Asthma*. 2017;54(6):584-593. doi:10.1080/02770903.2016.1244828
18. Busse WW, Holgate S, Kerwin E, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med*. 2013;188(11):1294-302. doi:10.1164/rccm.201212-2318OC.