Overview

Welcome to this activity on the role and use of targeted therapy with monoclonal antibodies for the treatment of patients with severe uncontrolled asthma. This activity focuses on addressing the difficulties encountered by clinicians regarding the selection and use of the 5 monoclonal antibodies currently approved for severe asthma in the United States. Based on a discussion of the differences between severe and uncontrolled asthma, this activity takes a deep dive into asthma phenotypes, including the role of biomarkers, and how this information is used to select biologic therapy. Clinical criteria for assessing treatment response are also discussed.

Target Audience

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

Learning Objectives

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

- Appraise the latest developments, including monoclonal antibody therapies, in the treatment of patients with severe uncontrolled asthma
- Differentiate between currently available monoclonal antibody therapy for severe uncontrolled asthma
- Assess and integrate factors determining the choice of monoclonal antibody therapy for patients with severe uncontrolled asthma

Faculty

Jonathan Corren, MD
Clinical Associate Professor of Medicine and Pediatrics
Division of Clinical Immunology Allergy, Co-Director
UCLA Nasal and Sinus Disease Center
Medical Director, Allergy Research Foundation
Los Angeles, California

Reynold A. Panettieri, Jr, MD
Vice Chancellor, Translational Medicine and Science
Director, Rutgers Institute for Translational Medicine and Science
Professor of Medicine, Rutgers University
New Brunswick, New Jersey

Emeritus Professor of Medicine, University of Pennsylvania

Accreditation and Certification

The Annenberg Center for Health Sciences at Eisenhower is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Annenberg Center for Health Sciences at Eisenhower designates this enduring material for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

AANP PROVIDER | American Association of NURSE PRACTITIONERS

Annenberg Center for Health Sciences at Eisenhower is accredited by the American Association of Nurse Practitioners as an approved provider of nurse practitioner continuing education. Provider number: 040207.
This program is accredited for 1.0 contact hour.
Program ID #5811-EM1

Disclosure Statement

It is the policy of the Annenberg Center for Health Sciences to ensure fair balance, independence, objectivity, and scientific rigor in all programming. All faculty and planners participating in sponsored programs are expected to identify and reference off-label product use and disclose any relationship with those supporting the activity or any others with products or services available within the scope of the topic being discussed in the educational presentation.

The Annenberg Center for Health Sciences assesses conflict of interest with its instructors, planners, managers, and other individuals who are in a position to control the content of CE/CME activities. All relevant conflicts of interest that are identified are thoroughly vetted by the Annenberg Center for fair balance, scientific objectivity of studies utilized in this activity, and patient care recommendations. The Annenberg Center is committed to providing its learners with high-quality CE/CME activities and related materials that promote improvements or quality in health care and

not a specific proprietary business interest of a commercial interest.

In accordance with the Accreditation Council for Continuing Medical Education Standards, parallel documents from other accrediting bodies, and Annenberg Center for Health Sciences policy, the following disclosures have been made:

Jonathan Corren, MD
Research Support: AstraZeneca – clinical area: Asthma, Genentech/Roche – clinical area: Asthma, nasal polyps, Novartis – clinical area: Chronic urticaria, Regeneron – clinical area: Asthma, eosinophilic esophagitis, Sanofi – clinical area: Asthma, eosinophilic esophagitis

Consultant: AstraZeneca – clinical area: Asthma, Genentech/Roche – clinical area: Asthma, nasal polyps, Novartis – clinical area: Chronic urticaria, Regeneron – clinical area: Asthma, eosinophilic esophagitis, Sanofi – clinical area: Asthma, eosinophilic esophagitis

Speakers Bureau: AstraZeneca – clinical area: Asthma, Genentech/Roche – clinical area: Asthma, nasal polyps, Novartis – clinical area: Chronic urticaria, Regeneron – clinical area: Asthma, eosinophilic esophagitis, Sanofi – clinical area: Asthma, eosinophilic esophagitis

Reynold A. Panettieri, Jr, MD
Research Support: AstraZeneca, MedImmune, RIFM, Equillium, Genentech, Metera, clinical area for above: Pulmonary Disease

Consultant: AstraZeneca, MedImmune, RIFM, Equillium, Theravance, Avillion, clinical area for above: Pulmonary Disease

Speakers Bureau: AstraZeneca, Sanofi, Genentech, clinical area for above: Pulmonary Disease

The faculty for this activity have disclosed that there will be discussion about the use of products for non-FDA approved indications.

Additional content planners
The following have no significant relationship to disclose:
Juan Cardet, MD (Peer Reviewer)
Gregory Scott PharmD, (Medical Writer)
Heather M. Jimenez, FNP-C (Nurse Planner)

Annenberg Center for Health Sciences
All staff at the Annenberg Center for Health Sciences at Eisenhower have no relevant commercial relationships to disclose.

The ideas and opinions presented in this educational activity are those of the faculty and do not necessarily reflect the views of the Annenberg Center and/or its agents. As in all educational activities, we encourage practitioners to use their own judgment in treating and addressing the needs of each individual patient, taking into account that patient's unique clinical situation. The Annenberg Center disclaims all liability and cannot be held responsible for any problems that may arise from participating in this activity or following treatment recommendations presented.

This educational activity is supported by an educational grant from GlaxoSmithKline

This activity is an online enduring material. Successful completion is achieved by reading and/or viewing the materials, reflecting on its implications in your practice, and completing the assessment component.

The estimated time to complete the activity is 1.0 hour.

This activity was released on July 31, 2020 and is eligible for credit through July 30, 2021.

Our Policy on Privacy
Annenberg Center for Health Sciences respects your privacy. We don't share information you give us, or have the need to share this information in the normal course of providing the services and information you may request. If there should be a need or request to share this information, we will do so only with your explicit permission. See Privacy Statement and other information at http://www.annenberg.net/privacy-policy/

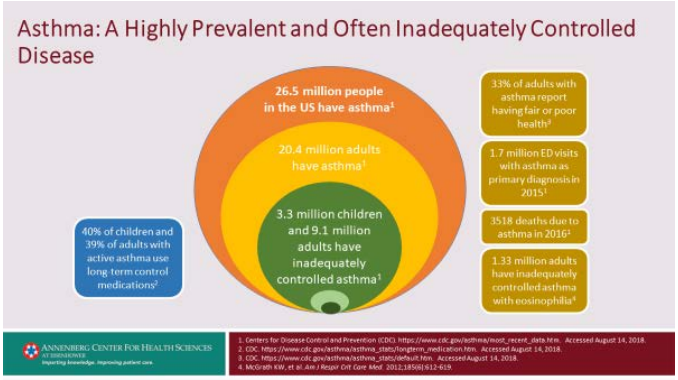
Contact Information
For help or questions about this activity please contact Continuing Education:
ce@annenberg.net

Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

Editor's Note: This is a transcript of a webcast presented on July 9, 2020 at Eisenhower Health, Rancho Mirage, California.

Jonathan Corren, MD: So the title is "Severe Uncontrolled Asthma and Monoclonal Antibodies." So from our title, you can see where we're heading with this. We'll be focusing on some very specific therapies for the most refractory patients. I helped develop this slide set with Rey Panettieri, who's out at Rutgers, New Jersey, and as you can see, these are my disclosures (see CE Statement for disclosures). I've worked with a number of pharmaceutical companies as a consultant and as a researcher to try to help develop some of the therapies we're going to be hearing about today.

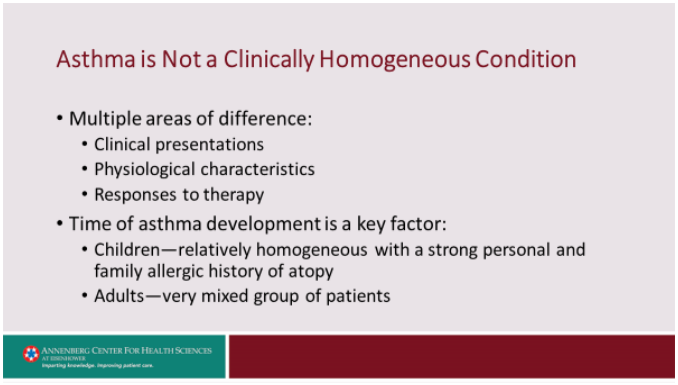
So what we're going to start with is trying to get a handle on appraising the latest developments, including monoclonal antibody development. We're going to talk about the differences between these antibodies and we're going to try to integrate not only factors relating specifically to these treatments, but sort of a global approach to patients who are the worst of the asthmatics.



We'll start with some epidemiology and statistics. If we start with the outer orange circle, we can see that it's been estimated that around 27 million people have asthma in the United States. The majority of these are adults and a smaller number of children. But at the end of the day, the green circle shows us that there are millions of people who have uncontrolled asthma, despite good adherence to their inhalers and other oral therapies that may be available.

If we kind of look at these boxes, it will help us characterize and flush out what's going on with these patients, but a third of adults have what they consider to be fair or poor health that they attribute to their asthma. There are over 1.5 million emergency room visits per year, primarily on the basis of asthma, dating back over the last 5 years. And there are still a few thousand deaths attributed to asthma on a yearly basis. If people were to be assessed using an ACT test or an ACQ, almost 2 million people consider themselves to have inadequately controlled asthma, along with eosinophilia, so that becomes an important aspect, because that opens up a particular avenue of therapy.

When we look at how many people really are using medications, around 40% of both children and adults who have asthma are on some kind of a long term controller and one of the questions is should there be a greater number of patients being treated with maintenance therapy than are currently receiving it?

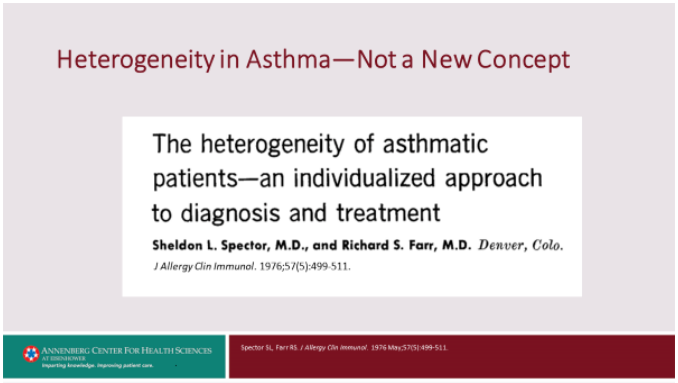


So, we're going to start with the concept that asthma is not monolithic. In other words, it's not like an infection like influenza where there's really one influenza and people get it and there are a variety of responses to it, but asthma really is a group of syndromes where there may be differing clinical presentations, there may be differing physiologic characteristics, particularly with respect to how severe obstruction may be. A very big area that we've really explored is how different the responses to therapy may be.

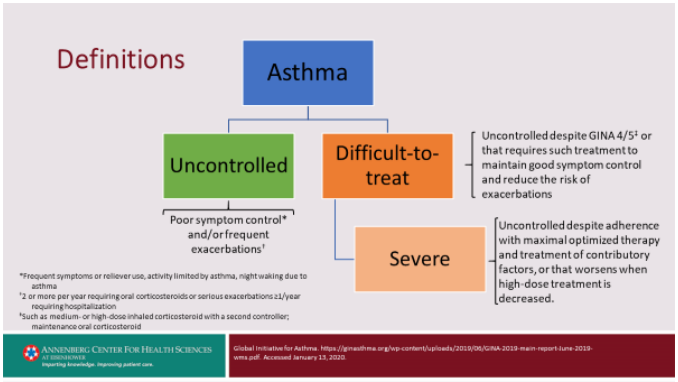
If you develop asthma as a child, typically that's a much more homogeneous disease. It's typically allergic in up to 90% of cases. It's usually preceded by atopic

Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

dermatitis and allergic rhinitis and there's usually a family history of atopy. When people develop asthma in their late 20s into their 30s, you're looking at a very mixed and heterogeneous group of patients.

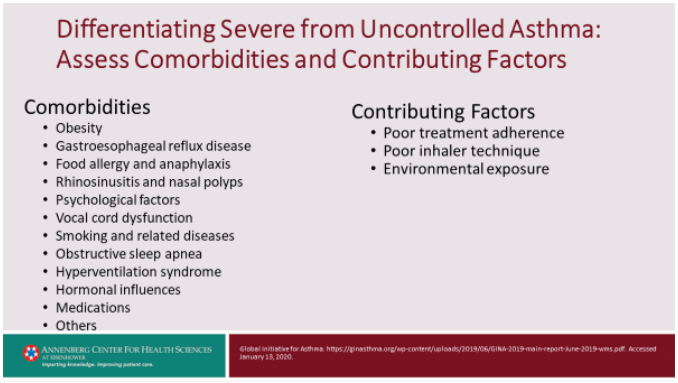


This was remarked upon going back over 40 years ago. This was an article written by my partner, Sheldon Spector, who unfortunately is recently deceased, and his mentor, Dr. Farr, who entitled an article The Heterogeneity of Asthmatic Patients - An Individualized Approach to Diagnosis and Treatment. For many, many years, even decades, we've recognized that there are particular characteristics in groups, but we really haven't hit upon that and understood it until, I would say, the last five years.



So some of the definitions. We have asthma. We've got uncontrolled asthma, which are people that basically continue to have exacerbations and frequent symptoms and we have difficult to treat asthma. Difficult to treat asthma may be difficult to treat because patients primarily may have comorbid conditions that are going undiagnosed and untreated, things like gastroesophageal reflux or sinus disease.

But from that difficult to treat group, there's a subset who you've ruled out: poor adherence, you've ruled out reflux, you've ruled out sinus disease, you've ruled out concomitant recurrent bronchial infections and they have bad asthma. This group of patients is basically in search of a better therapy, and that's what we're going to be talking about today.



So we talked about difficult to control asthma, and we have to always consider the effects of concomitant morbid conditions. Obesity is a big one. 40% of the American population is overweight or obese and this can fuel asthma both from the point of view of physiology with pushing up to the diaphragm in a relative state of restriction, but obesity is also an inflammatory state. The whole metabolic syndrome gives rise to things like interleukin 6 and leptin coming out of adipocytes, which can up-regulate inflammation in the lung.

Reflux disease, often times not asked about, and plenty of data shows that there's a lot of reflux in patients with asthma. Food allergy, more of an issue in children. Rhinosinusitis and nasal polyp disease. It's sort of the upper airway corollary of asthma, and because of the constant drainage and recurrent infections, can make asthma very difficult to manage.

Psychologic factors, like anxiety and depression, may make the perception of symptoms worse. It may also be an obstacle to good adherence. Vocal cord dysfunction. What is it? Adduction of the vocal cords during inspiration, you get closure. So these people very often will mimic severe asthma, but they usually say their asthma consists of difficulty breathing in rather than

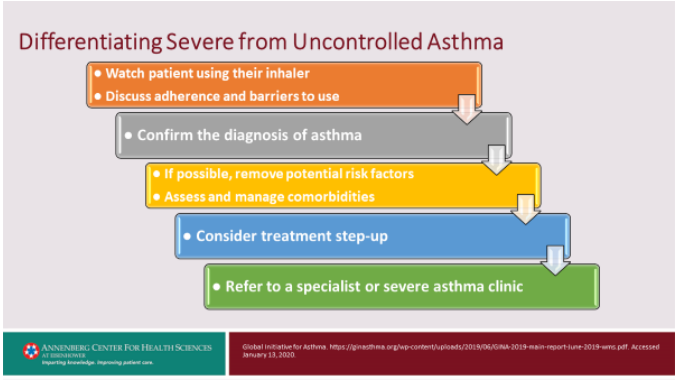
Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

breathing out, and these people often have comorbidities of reflux and postnasal drip. Smoking can make people resistant to steroids. Sleep apnea can aggravate asthma. Of course, there's hyperventilation syndrome, where there isn't even asthma present, and it's more of a psychic condition.

Hormonal influences. We often don't think about it, but women can have menstrual flaring of asthma due to the effects of female hormones and these may be exceptionally difficult to treat. You should always think about medications, particularly beta blockers, which may be impairing asthma, or ACE inhibitors, which increase cough and can be mistaken for asthma.

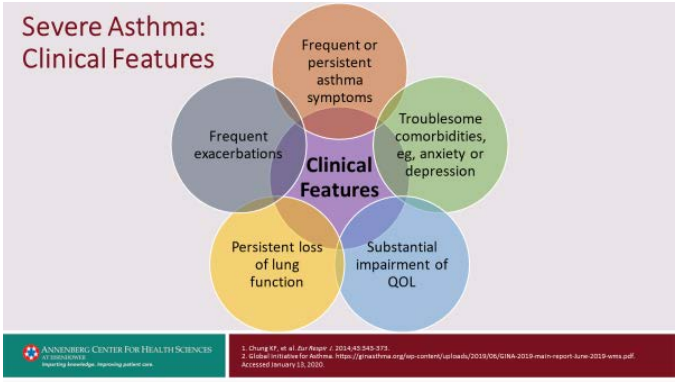
These are the comorbidities. What are the contributing factors? Things that are in the hands of the patient. They don't adhere to their therapy. They are taught to use their inhaler and don't continue to do it correctly. A quick statistic is that 25% of patients consistently use their inhaler correctly. When you train them, it goes up to 90% to 95%, but if you don't reinforce it consistently, 3 months later it's down to 25%.

Finally, environmental exposures. How many of us have talked to patients who have entered a workplace where there were work stations and some of those stations may have had a pet dog, or they get married to someone with a pet cat, and these kinds of environmental influences, superimposed on their chronic disease, can make things very difficult to control.



When we talk about the differentiation of severe asthma from uncontrolled asthma, some of the things that we need to do are watch the patient using their inhaler and actually go so far as to investigate their adherence by checking pharmacy refills. We should always remember to confirm the diagnosis of asthma using pulmonary function testing. So if a patient says, "I think I whistle when I breathe and I cough a lot," there's a tendency to want to diagnose it as asthma and it may be asthma, but we should always do spirometry pre and post bronchodilator.

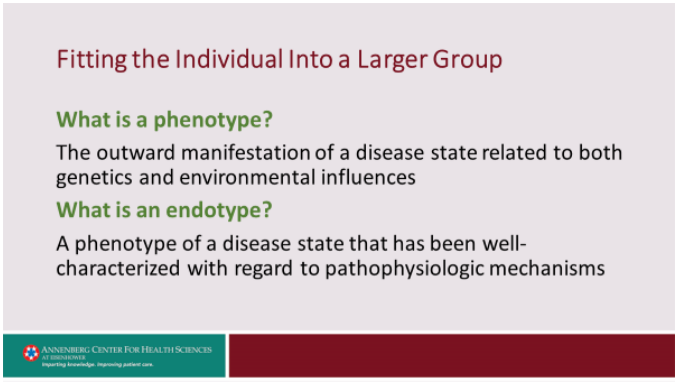
If we can and we've confirmed it as asthma, think about the things that are potentiating it. When we've ruled out all of these things and they're on maintenance therapy, let's say they're on a low or a medium dose of ICS with or without LABA, consider stepping up to combining it with a LABA. And then when all else fails and you've done your due diligence as an internist or as a non pulmonary non allergy subspecialist, remember that there are people that can certainly join you in the treatment of these patients and help you with these more difficult cases.



What are some of the features of severe asthma? Let's start at the top. Frequent or persistent symptoms. Typically when we call it severe uncontrolled, it's daily, with symptoms at night many nights per week. There are frequent exacerbations, as we rotate counterclockwise. There may be persistent loss of lung function. When we look at clinical trials, and this applies to my own experience in my asthma clinic, of patients who have severe asthma and they're entered to be tried on a new medication, typically their lung function is in the low 60s. So it's not unusual for these people to live between 60% to 65% of predicted and along with that

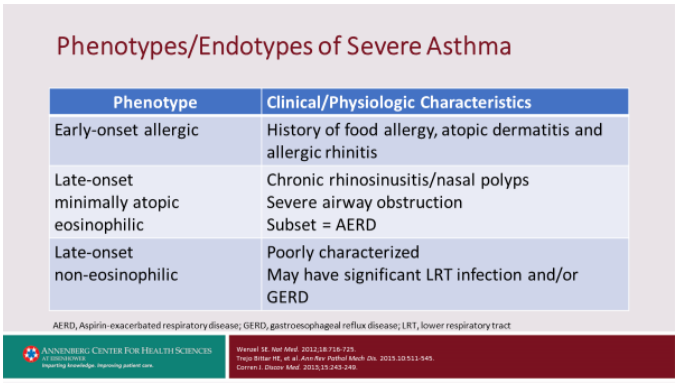
have a substantial impairment of quality of life, which we see here in blue.

Then, at the end of the day, these people may have concomitant comorbidities that are there, maybe adding to the severity, but even when you remove it, the patient still has severe asthma. I think the best example of this are some of the psychiatric comorbidities, in which case the asthma may make their anxiety and depression worse. When you actually treat the asthma adequately, we find that their depression and anxiety may both abate significantly.



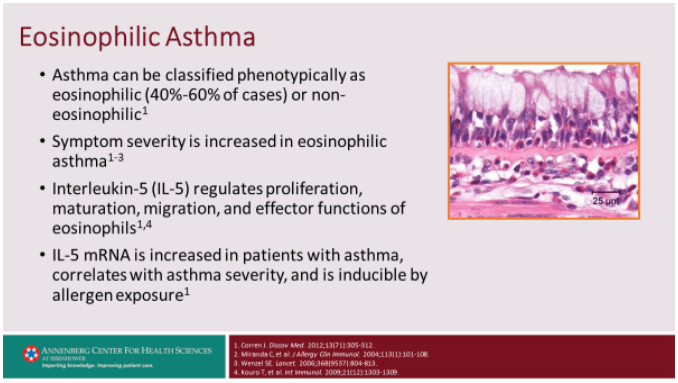
Let's get back to this idea that we've diagnosed the patient with asthma, we're certain that it's asthma. We did pulmonary function testing. We've looked for other comorbid conditions that could mimic asthma. We're trying to understand, where do they fit into the overall scheme of asthma. So we ask ourselves the first question, what is a phenotype? And what is a phenotype of a given patient with asthma?

We understand that a phenotype is an outward manifestation of a disease. First of all, it's regulated genetically, but it's also regulated environmentally. We even know that the environment can regulate the genetics and this is an area called epigenetics. But if we go beyond the phenotype and we try to understand what's driving this phenotype pathologically, this gives rise to the concept of an endotype. An endotype is, as an example, a patient with aspirin-sensitive asthma, or we sometimes call it Samter's triad or aspirin exacerbated respiratory disease, and we have really identified that these people have lots of eosinophils and lots of leukotrienes that we can measure even in the urine and identify. So that's a good example of an endotype, and an endotype is important, because that's going to tell us how to treat the phenotype.

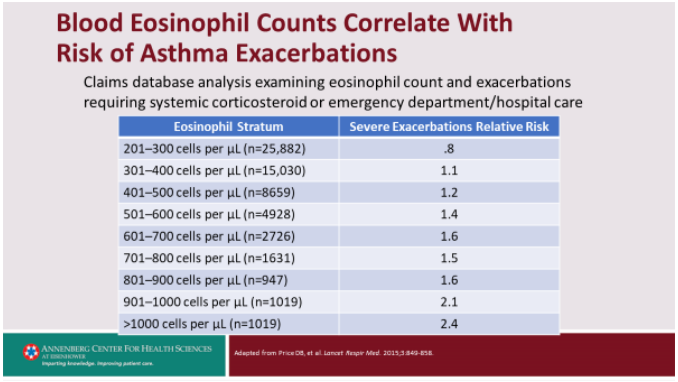


Some of the phenotypes that have been well characterized are early outset allergic asthma. As I mentioned earlier, these people have food allergy very often in the first year of life, with eczema. They may progress to allergic rhinitis and then ultimately, sometime before age 10, develop asthma. Then we've got a late onset form of asthma. These people are eosinophilic, but they're not allergic. We'll explain that later when we talk about some of the pathophysiologic pathways. These people oftentimes have chronic rhinosinusitis with nasal polyps. They often have very severe airways obstruction, shockingly low in some cases, down in the 40s. A subgrouping of these people have aspirin exacerbated respiratory disease, which I just touched on a moment ago. So they have polyps, they have eosinophilia in the blood, they have severe asthma, and when they take any kind of a nonsteroidal, they have a severe flareup of the asthma. Finally, the group that we call late onset non-eosinophilic. Very poorly characterized. These people, in my experience, often have lower respiratory tract infection, sometimes upper respiratory tract infections and/or acid reflux.

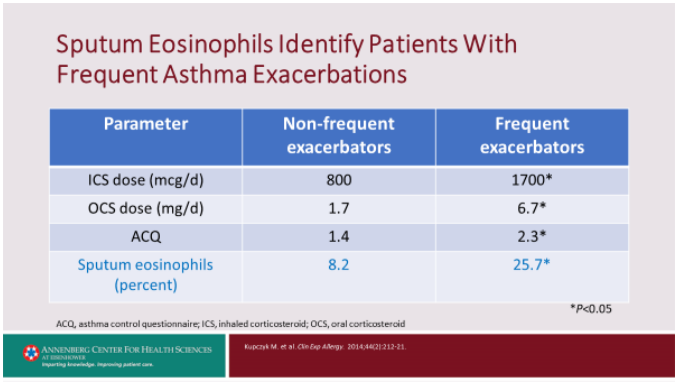
Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1



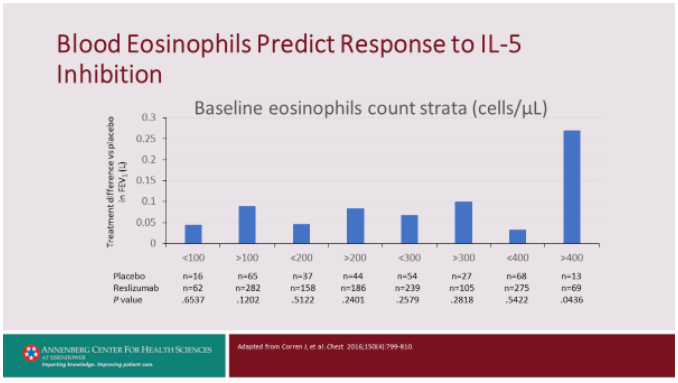
So let's now focus on eosinophilic asthma. It turns out around half of patients that you're going to see who have severe asthma have this eosinophilic form. About half will have non-eosinophilic. If we look at the people with eosinophilic asthma, typically they are the worst, and the more eos they have, the worse they do. What regulates the eosinophil is a single cytokine that seems to have the most impact on this process, which is interleukin 5. Many of you are aware of interleukin 5. We know there are now drugs which block interleukin 5. Interleukin 5 is the key factor in causing the maturation of eosinophilic progenitor cells, causes them to proliferate, ultimately to migrate up into the airway, both the lower and the upper airway, and it carries out the effector functions of these eosinophils. So IL-5, we know is increased in patients with asthma. It correlates with severity and it may be induced either by allergen exposure or sometimes by the factors which we can't identify. Here's a great example.



This is from *Lancet*. David Price published this. It's probably the best data. Lots and lots of patients. He broke it down by eosinophil levels, starting with 200, and each of these has a 100 eosinophil increment. At the bottom it's greater than 1000. On the right, you can see the relative risk for severe asthma exacerbation. We can see that between 200 and 300 you're at sort of a baseline level, which would be around 1.0. But as you go up higher and higher, that proclivity, particularly in the very realms, 800 and above, you get into up a doubling or 2½ fold increase of exacerbations over a group of patients who are control.



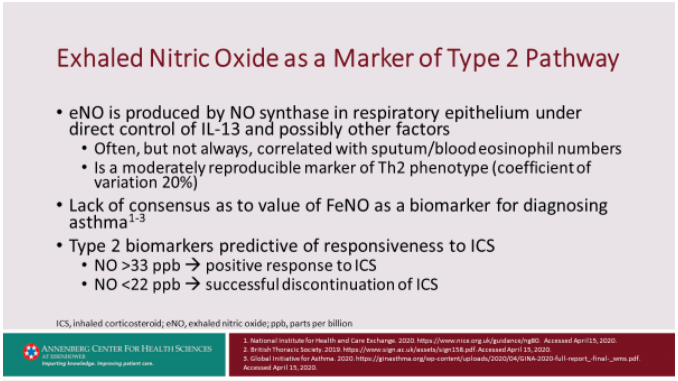
Another way of looking at this is through the sputum and this was through a European collaborative study, where they found that blood eosinophils are useful, but if you look at sputum eosinophils, there are a group of severe patients who have more than 2 or 3 exacerbations per year and if you can't get a good measurement on the blood, for whatever reason, always realize that sputum is an even better predictor, and these people who had about 25% sputum eosinophils had lots of exacerbations compared with the non frequent exacerbators who were down at 8%.



One of the things we've learned is that an eosinophil count is a very good predictor to the effects of IL-5 inhibition. Here we're using FEV-1 as the measure.

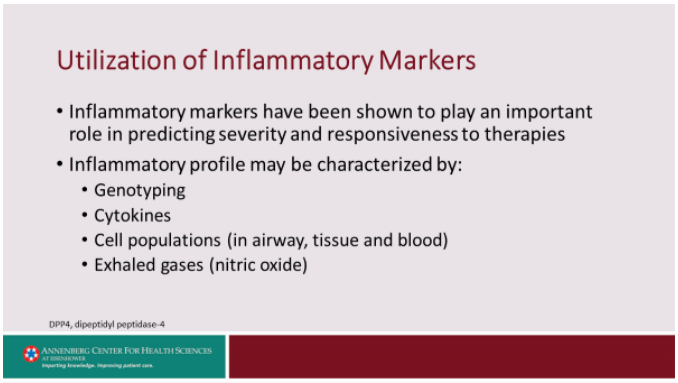
Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

We're looking at less than or greater than 100 eosinophils in the blood, less than or greater than 200, less than or greater than 300 and finally less than or greater than 400. We find that when we use 100 as a split point, it's not a very good differentiator. You have to go all the way up to 400. This is where you really see giving an IL-5 inhibitor like reslizumab or mepolizumab or benralizumab, which we'll talk about in a minute, is a very good differentiator to determine who had the real improvement in pulmonary function. For exacerbations, it's not quite as high as 400. For exacerbations, probably a good break point is around 300. What it tells us is that if you don't have a certain number of eosinophils that have to be present, not at the time of the visit, but sometime in the past year, and the more reproducible it is the better, then you're going to get a response to these drugs. And in the absence of this, you're not going to.



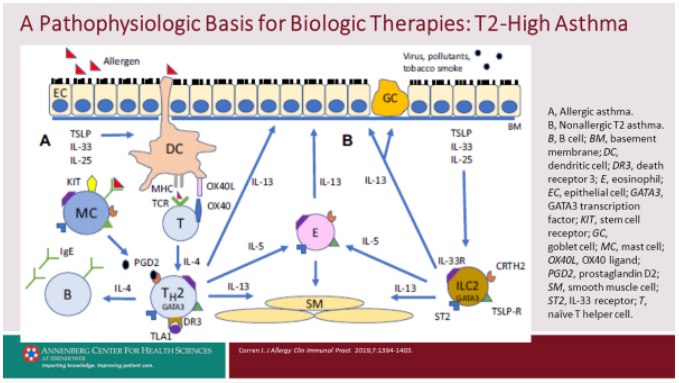
What about exhaled nitric oxide. I don't know how many of you measure this in your own clinics or your pulmonary function lab, but exhaled nitric oxide is a gas that we can measure in the expired air. It comes from the respiratory epithelium and it's under the control of interleukin 13. That's the primary determinate. There is a good correlation, but not always, with sputum and blood eosinophils and it's a pretty reproducible marker of what we call the TH2 or type 2 phenotype. The type 2 phenotype is a reflector of both IL-13 and IL-5, which we've just talked about. To lesser extent, IL-4. So what we're trying to do with these biomarkers is detect is there IL-13 or IL-5 present in the blood and tissue of these patients and then it tells us what to block. So if somebody had a very high IL-13, they would have a very high exhaled nitric oxide and we would want to block IL-13. We'll get into some of the nitty gritty of that.

So there's a lack of consensus about how we use this biomarker for diagnosing asthma, but certainly it's a biomarker for detecting if somebody has IL-13, if they're a type 2 asthmatic and their response to inhaled and oral steroids. So if somebody has an NO of greater than 33 parts per billion, they have a very good response to inhaled corticosteroids, whichever you pick, and if it's less than 22, you can stop inhaled steroids and probably not want to start them in somebody who's a de novo new diagnosed asthmatic. So if somebody comes into you, you work them up, they have asthma, their NO is 14 and they don't have a lot of blood eosinophils, interestingly they're not going to get much better on inhaled or oral corticosteroids.



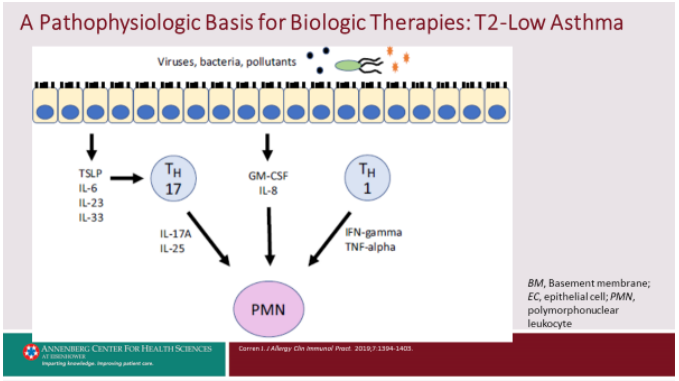
So let's talk about inflammatory markers. They play a role in predicting severity and responsiveness to therapy. We just touched on that. There's a number of ways you do it. You can do phenotyping. You look at cytokines in the blood. Both of these are not easy. This is something we relegate really to the research lab. Cell populations in the airway tissue or blood and exhaled gases like nitric oxide.

Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1



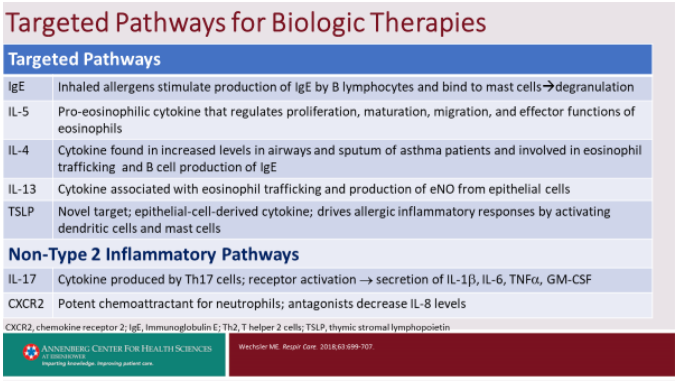
So this is a complicated schema, but if we kind of walk through it, we see there are dendritic cells which are sampling allergen, that little red triangle, which is actually in the lumen of the airway. The patient's inhaled the allergen, the dendritic cell actually pokes it's pseudopod through the epithelium, it samples it, it then interacts with a naïve T-cell if the person is genetically predisposed and they go on to form an allergen specific TH2 cell.

If we look, I want you to focus on that relationship between the TH2 cell and the E, which is the eosinophil. But if you move to the right, we can see that there's a brown cell called the ILC2, or the innate lymphoid cell type 2, which also releases IL-5 and can bring in eosinophils, but this is without allergen exposure. So the question is what can stimulate that ILC2 cell to create an eosinophilic milieu in the airway of that patient. Some of the things that have been suggested, maybe tobacco smoke, maybe some other airway pollutants, maybe even viruses in selected patients. There may be a genetic component where somebody is not allergic, but still capable of triggering this whole eosinophilic axis.



Now, we've talked a little bit about what if they're non-eosinophilic and they have a low exhaled nitric oxide? What do we really do with that patient? And why do they have the disease? Here, we think infections play a much bigger role. Pollutants may play a role. And, as you can see, this is sort of some of the speculation about what are the cytokines that are causing this. It starts off with the release of these cytokines on the left. What I'd focus on really would be TSLP and IL-6, because we have antagonists for both of these. Tezepelumab, the antagonist is currently in development. In IL-6 we have Actemra, which is interestingly being used to block the cytokine storm of COVID-19. These factors seem to bring in TH17 cell population and, by the release of IL-17 we get neutrophils.

Going back for a moment. This is an eosinophilic, what we call type 2 disease. This is a neutrophilic very often non-type 2 disease. As you can surmise, these have to be treated completely differently because there's a completely different target cell. We'll talk about that.

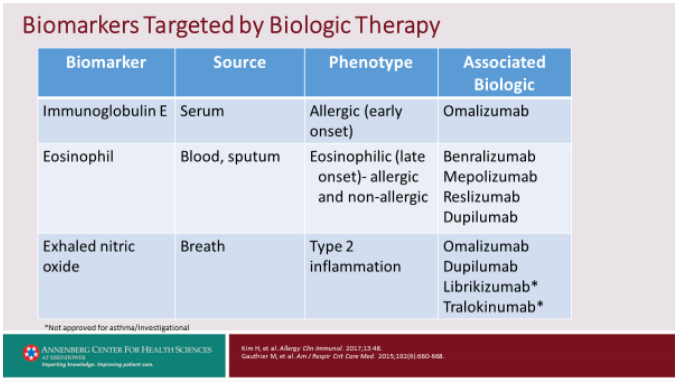


Some of the targeted pathways, IgE, we know that IgE is produced by B-cells, binds to mast cells. We have a blocker for IL-5. We've talked about how it's important to eosinophilia. IL-4 and IL-13 typically travel together. They're very similar and they have an effect both on the ingress of eosinophils into the airway, they have an effect on basement membrane thickening, on mucus secretion and ultimately on the production of IgE.

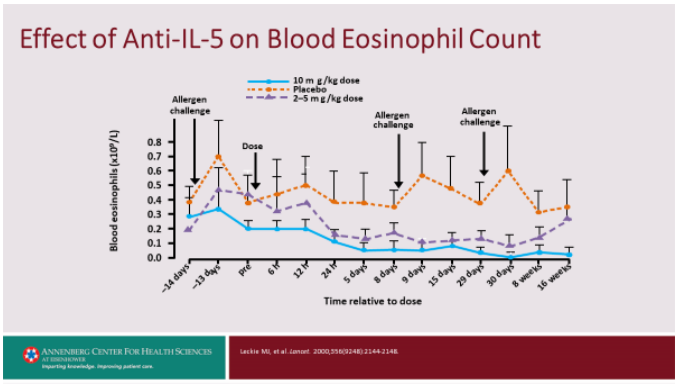
TSLP is a new target. Looking back again, we can see that TSLP comes from the epithelium and helps regulate

Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

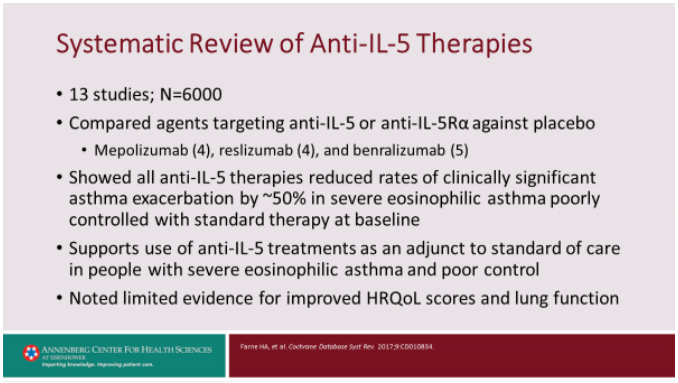
that dendritic cell to cause T-cells and ILC2 cells to become eosinophilic prone. The non-type 2 pathways are the ones we're really getting a handle on. IL-17, we've touched on. That seems to be very important in terms of neutrophilic asthma. We also have CXCR2, which is a chemoattractant for neutrophils and seems to interact with interleukin-8.



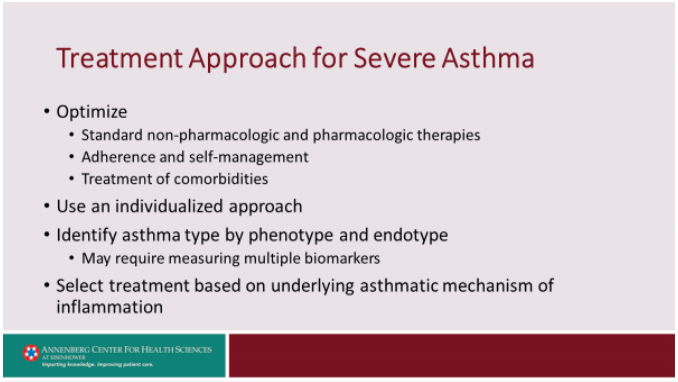
Biomarkers targeted by biologic therapy. IgE we know is targeted by omalizumab, eosinophils by benralizumab, mepolizumab, reslizumab and dupilumab and exhaled nitric oxide, which is an indicator of IL-13. Let's talk about this. Omalizumab seems to target the pathway but in an indirect way, by stopping mast cell degranulation. Dupilumab is a direct IL-4, IL-13 blocker at the receptor. Lebrikizumab and tralokinumab were both IL-13 inhibitors which did not make it through the phase 3 development programs to approved drugs, so that's why they're asterisks. So really the drug that really directly antagonizes IL-4 and IL-13, and hence the biomarker nitric oxide, is dupilumab.



So, what happens given anti-IL-5 and in this case it's mepolizumab and we can see that there's an allergen challenge and in orange we're looking at the effect of placebo. We're looking at 2 different doses of mepolizumab. Let's focus on the 10 mg/kg dose. We can see that within about a week you get rid of most of your eosinophils and by 8 to 16 weeks you've virtually got none there, and that applies really to most, if not all, of the anti-IL-5 drugs.



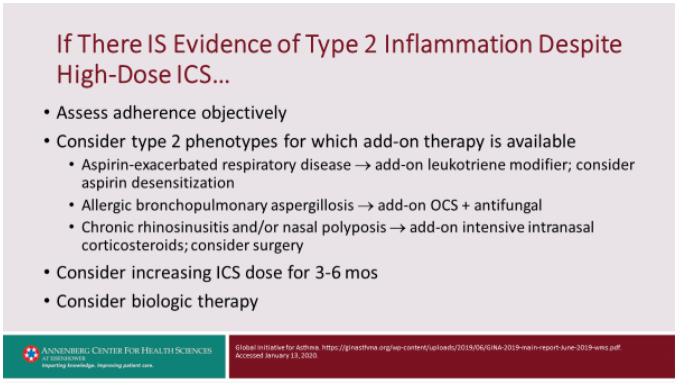
So if we take all the anti-IL-5, mepolizumab, reslizumab and benralizumab, there have been a number of studies for each. In the aggregate, they reduce exacerbations by about 50% of patients who have severe eosinophilic asthma or very poorly controlled with the highest doses of ICS-LABA, very often with tiotropium added on board and very often with the leukotriene antagonist on board. So, that kind of gives us an idea. What I will tell you is that if you do subsets of this, you look at people who are above 500 eosinophils, that that 50% reduction can be as high as 70%. There is good data showing that there are improvements in patient reported outcomes and improvements in lung function, although it was not highlighted in this particular meta analysis from the Cochran group.



Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

So what do we do when you're in the clinic and you're facing a patient who has relatively severe asthma? Well, we always want to remember that maybe this is a nonadherent patient, so we're going to try to standardize their pharmacologic therapy by watching them use the medication, by making sure they're filling it, by checking with the pharmacy and to make sure that they're doing nonpharmacologic methods, that if we've documented that they're allergic to a cat or dog, or something else in their environment, that that is being dealt with. And then finally that we consider their comorbid conditions. Now, if you take somebody and you presumptively call them a reflux patient in the absence of symptoms and you treat that with the proton pump inhibitor, a study done in children and adults, both published in the *New England Journal of Medicine* failed to show any improvement in patients who have severe asthma, unless there is detectable clinically manifest acid reflux.

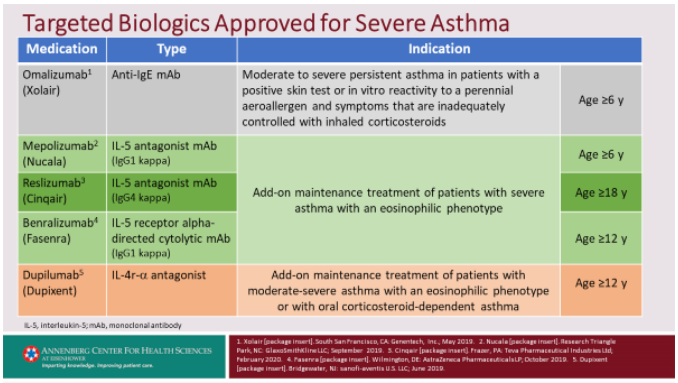
So keep that in mind. Reflux, chronic sinusitis, sleep apnea. You have to really run the gamut with these people and make sure that whatever comorbid condition they have is being treated. Always look at each patient as an individual. Consider all these factors and then try to do a basic phenotyping and endotyping by getting a blood count with a differential for eosinophils, by getting an exhaled nitric oxide if you can. Then based on this information, we can talk about therapies.



So we've talked about assessment of adherence. Let's say you have a person with aspirin-exacerbated respiratory disease. This is a great population to try a leukotriene modifier. My own preference is for 5LO inhibitors, which is zileuton. The leukotriene receptor antagonists like montelukast and zafirlukast are good, but not quite as good. Something that we can always consider in these patients is aspirin desensitization through an allergy immunology clinic.

Think about ABPA. We know that antifungals play a key role in these patients. They may need bursts of steroids. We're now considering biologics in these patients and we do have an article that's been submitted in that regard.

Finally, how do you deal with rhinosinusitis and nasal polyposis? Intensive nasal corticosteroids. Consider surgery if they have very large polyps. Now we have one approved biologic, dupilumab, for this indication, and there seems to be data for mepolizumab, which is soon going to enter the public realm. There was a press release recently. Then consider increasing inhaled corticosteroid dose for periods of time. At the end of the day, consider a biologic therapy when you've considered all these other tweaks and nothing's working.



So these are some of the specific regarding the various biologics. With omalizumab, you need to have a positive skin test or an IgE to a perennial allergen, and it needs to be relevant. By that I mean let's say the patient lives up in Lake Tahoe or maybe Big Bear Lake or Arrowhead. We know that altitude there really are no dust mites and that's the only allergen they have. Omalizumab probably wouldn't be a great choice. It's approved now down to age 6.

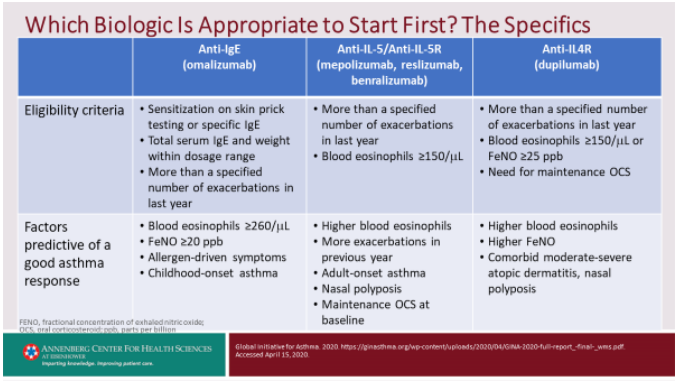
Severe Uncontrolled Asthma and Monoclonal Antibodies Part 1

Mepolizumab, they need to show eosinophilia. That's the main requirement. You can go as low as 150. The drugs work better above 300 and best above 500. Mepilizumab down to age 6. Reslizumab is an IV drug. It's the only IL-5 greater than 18. And benralizumab, which is a receptor antagonist does not bind to IL-5 and what makes it different is that it's given monthly for 3 months, like mepolizumab and reslizumab, but then after 3 months it's given every 2 months. Approved down to age 12. And then dupilumab is an IL-4 receptor alpha blocker, so it binds to the receptor. It binds to both IL-4 and IL-13 and blocks both of them. It's approved as add-on therapy for patients who have eosinophilic asthma, although if a patient had a low eosinophil count but an elevated exhaled nitric oxide, they would probably be a good case for starting this drug. I will say that for mepolizumab, benralizumab and dupilumab, they've all shown efficacy in oral corticosteroid dependent asthma and dupilumab is approved above age 12.

One of the goals, get rid of exacerbations or at least try to take them down significantly, improve the dally symptom burden and get them off oral steroids as soon as possible.

What's the right drug to start? That's a great question. It's a very nuanced question. I think we should always consider first the phenotype, which will be predictors of asthma response. So you're not going to start omalizumab in a nonallergic patient or a person with an irrelevant allergen. You're not going to start mepolizumab in a non-eosinophilic patient, nor any of the other IL-5 inhibitors. You should think about dosing frequency. So if somebody hates to give themself shots, and they travel a lot or there's some reason that they don't want to give it to themselves, think about the least frequent dosing possible.

Self administration now applies to most of these drugs. I'm going to go back up. Omalizumab is now allowing it. Mepolizumab is. Benralizumab is and dupilumab is. The only drug that doesn't is the IV reslizumab. And then patient preference. Patient preference will usually be a culmination of all of these things. But then we go back up to the top of the list, which says is it covered well by their insurance? This may be the most important factor at the end of the day. When you've picked your phenotype and you think you know what they'll respond to, not only have your first choice, but have your second and your third, because there may be differences in coverage.

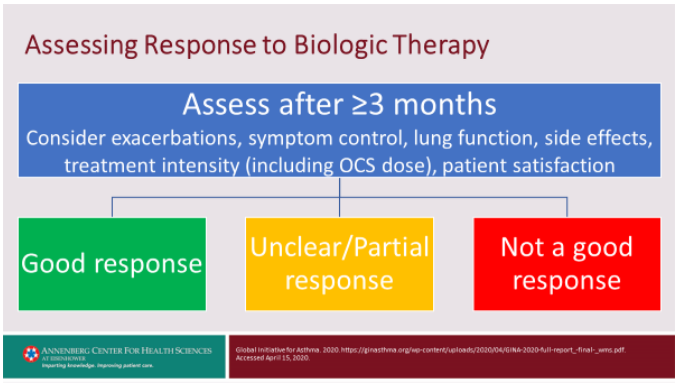


We've talked about what are the requirements. Whereas we talk about eligibility criteria for omalizumab, it's a positive skin or blood test. For both anti-IL-5 and anti-IL-4 receptor, it's eosinophilia and in the case of dupilumab it's also exhaled nitric oxide if the blood eos, which they may be in a small number of cases.

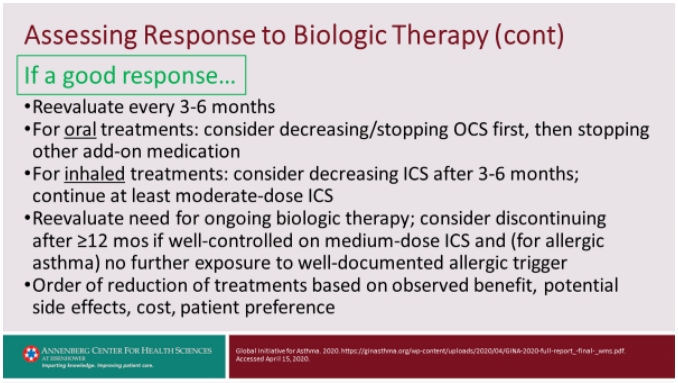
Now, let's look at what predicts a good response. With omalizumab, it's eosinophil count above 260 or pheno above 20. It's the fact that you have a relevant allergen in large supply and very often it goes better with people who have early onset disease. For the anti-IL-5 group and anti-IL-5 receptor, the higher the blood eosinophils, as we've talked about, the better they do. The sicker they are, the better they do. So if they come in with 6

exacerbations, there's a good chance you'll have an 80% reduction. Adult onset seems to do better than early onset. And the presence of nasal polyps is a predictor, so if they have polyps this is telling you there's a lot of eos, not only in the blood, but in the tissue. Then, maintenance oral steroids at baseline.

When we look at dupilumab, similar to the IL-5, here we mention you can use exhaled nitric oxide as one of the predictors. If you look at things that predict response, it's higher blood eos, higher pheno and comorbid conditions like atopic dermatitis and nasal polyposis. Once you've started, I recommend to give them probably a phone call in one month and back in the clinic in 3 to 4 months to see, are their symptoms better? That's the first thing you'll see. Is their lung function better?

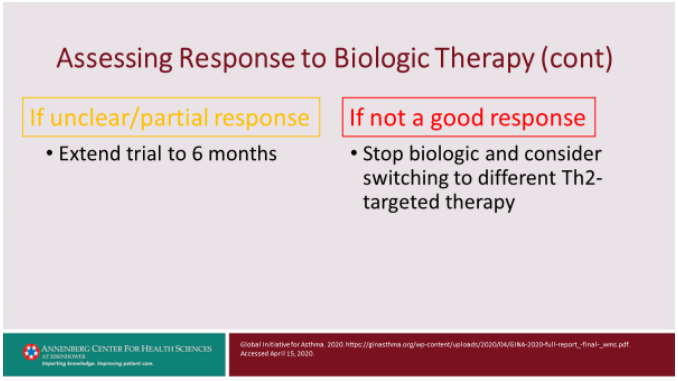


With all of these medications, which the exception of omalizumab, you should see an improvement in function. Are they having side effects? And when do you start to taper their oral steroids? Typically, I give them at least a month on medication, if not 2 months, and then start weaning it. You'll see in these patients either what you consider to be a good response, what we call the wow factor, they're happy; maybe a partial response, they're not really sure; and then finally, not a good response.



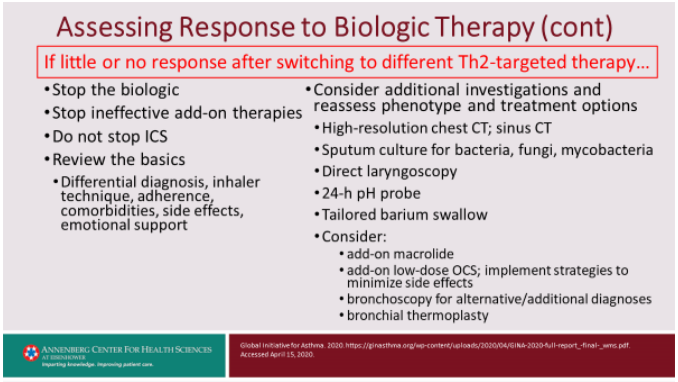
So what do you in a situation where particularly there's not a good response? It's not a good response. We'll talk about that in a moment. I probably would get rid of the drug. But if they do have a good response, look at them every 3 months through the first year, and then maybe every 6 months thereafter. If they're on oral steroids, that's the first thing you should get rid of. Getting rid of inhaled steroids may be an issue, especially if they're on high dose inhaled steroids, the highest dose that's prescribed for any of the agents. They may get bruising, they may get thrush, there may be absorption of the drug in high dosages, they may get cataracts or glaucoma. So secondarily I would try to get them to a lower dose of ICS.

If they stay on a low to medium dose of ICS, it's probably for the best, because there are insults that are addressed by ICS-LABA that they may not be well-addressed with the biologic.



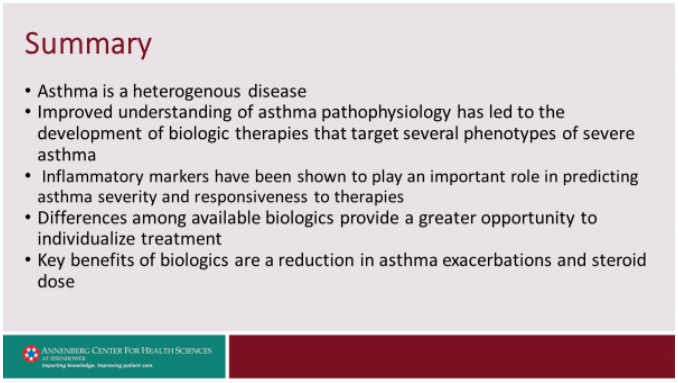
If there's a partial response when you've seen them at 3 to 4 months, give them another couple months, see how they do. But if after 3 to 4 months they're not doing well at all, I would get an eosinophil count, and

the reason being if they're a really large patient, high BMI and you had them on let's say mepolizumab and they didn't get the eosinophil count down low enough, then you might consider one of the other anti-eosinophilic drugs. But for the most part, mepolizumab, benralizumab and reslizumab will get the eosinophil count down pretty well with the 3 to 4 months of therapy and you really have to think about changing to another pathway blocker.



So here we have, I want you to focus on the right side, what do you do if they're really not doing well with a couple of biologics? You may want to move these things up earlier in the diagnostic evaluation. But think about getting a CT of the chest. Make sure that we're not dealing with emphysema that we missed. Think about getting a sinus CT. That may be fueling the asthma and we missed it. Think about getting a smear and a culture for atypicals, particularly fungi and mycobacteria. Consider laryngoscopy, looking for vocal cord nodules, polyps, evidence of reflux. If you really, really want to diagnose reflux, you could either do an endoscopy or a PH probe or tailored barium swallow.

Now, some of the things that we can do if a type-2 biologic doesn't work is we can think about using a macrolide, where there is pretty good evidence-based medicine. We could think about a low dose of oral steroids. I like to do this only for short periods of time. Consider doing a bronchoscopy, really getting into the lung tissue and trying to make an alternative diagnosis, particularly infection. And then if you have a good bronchoscopist, who does thermoplasty, this would be the time to really think about using that.



So, we've covered a lot of material today, starting with the idea that asthma is a very heterogeneous disease, and we really have developed a much better understanding of how these various pathways interact and how they cause these endotypes of asthma. We've come away with an idea that you have really 3 important cytokines that we're able to treat right now. We have IL-4 and 13, which can be blocked an IL-4/13 blocker, and we have IL-5 that can be blocked by 3 different therapies. We also have IgE, which can be blocked specifically by omalizumab in allergic patients.

Now how do you take this through the bedside? Through biomarkers. And we know that the ordering in our hands of things like blood eosinophil count and potentially an exhaled nitric oxide can provide very important information. And then finally there are key benefits of biologics that we've discussed which may be extremely important in asthma exacerbations and reducing patients' need for oral corticosteroids.