BIOLOGICS IN SEVERE ASTHMA: OPTIMIZING THERAPEUTIC SELECTION AND PATIENT OUTCOMES

OVERVIEW

This case-based activity focuses on considerations, including phenotypes and biomarkers, in individualizing treatment with the 5 monoclonal antibodies currently approved for severe asthma in the United States. The role of shared decision-making is discussed as an approach to individualizing therapy and improving patient outcomes. Clinical criteria for assessing treatment response to biologic therapy and how to modify therapy when needed are also discussed.

Target Audience

This activity was developed for pulmonologists, allergists, immunologists, primary care physicians, and other healthcare professionals involved in the care of patients with severe asthma.

Learning Objectives

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

- Discuss the latest evidence regarding the pathophysiology of severe asthma
- Explain the clinical implication of the latest scientific developments in the area of biologic therapies for the management of severe asthma
- Differentiate biologic therapies currently available for the management of patients with severe asthma
- Implement biologic therapy for a patient with severe asthma taking into account the latest available data and genetic factors

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The estimated time to complete the activity is 1.0 hour.

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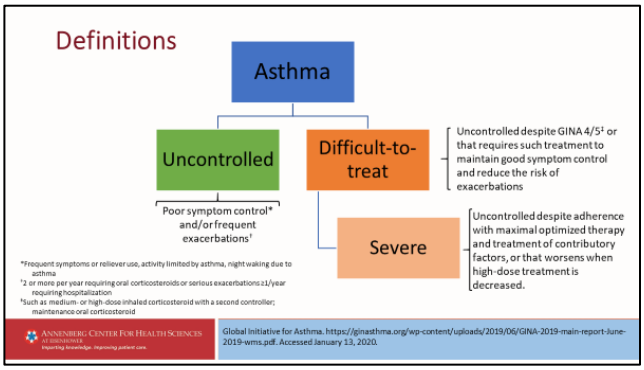
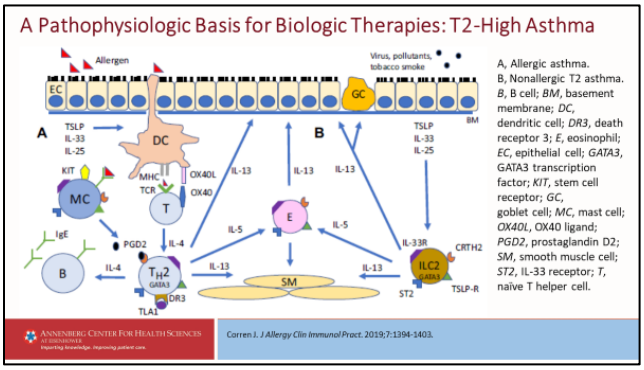
BIOLOGICS IN SEVERE ASTHMA: OPTIMIZING THERAPEUTIC SELECTION AND PATIENT OUTCOMES

Introduction: Asthma can occur either as uncontrolled or difficult-to-treat. And within the difficult-to-treat group, there's the severe asthma. Now, what is uncontrolled? Well, that is poor symptom control and/or frequent exacerbations. So, how does that differentiate from difficult-to-treat? Well, difficult-to-treat asthma is uncontrolled despite GINA 4 or 5 guidelines, or that requires such treatment to maintain good symptom control and reduce the risk of exacerbations. So, what is severe asthma? Well, severe asthma is uncontrolled despite adherence and maximal optimized therapy and treatment of contributing factors; often requires high-dose therapy and sometimes oral corticosteroids.



Case #1: A 56-year-old man is being seen for routine follow-up of asthma, hypertension, and type 2 diabetes. He appears to be in some distress, with evidence of wheezing and mild shortness of breath. Noted to sneeze frequently during the exam. His physical exam showed inspiratory wheezing, and bilateral rales and nasal congestion. Again, he had hypertension, type 2 diabetes, and has come in for routine follow-up of his asthma.

So now let's examine the pathophysiology potentially related to that case #1. On this slide, we highlight, in a cartoon, T2-high asthma. Now, what is T2-high asthma? T2-high asthma actually is derivative of what we used to call Th2, which referred to a specific subtype of lymphocytes, that is the CD4 or Th2 lymphocytes. We now use the term T2-high asthma to encompass not only CD4 lymphocyte subsets, but mast cells, and the eosinophils. So, on the left side, we're looking at high T2 driven by allergens. Allergens are picked up by dendritic cells and antigen-presenting cell, that then moves to the regional lymphoid tissue and induces the proliferation of a subset of T cells, the Th2, or CD4 cells.



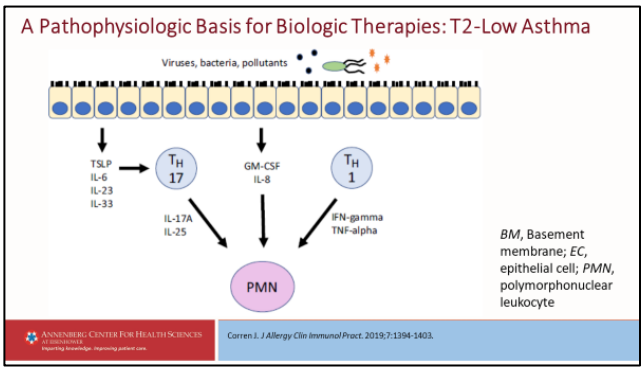
Now, these cells are very important because they secrete IL-4, IL-13, and IL-5. The IL-4 can convert a B cell to a secreting IgE cell. And the presence of IgE binding to an Fc-Epsilon high affinity receptor, typically found on mast cells and basophils, causes the secretion of preformed mediators, histamine, leukotriene B4, and others. These have direct effects on effector cells. Now, also, the epithelial cell is a rich source for alarmins. Damaged epithelium or activated epithelium will secrete thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. These are collectively members of the alarmin family and they, too, can communicate, amplify, and orchestrate inflammatory response. That's the high T2 sites.

Now, recognize that the IL-5 secreted by CD4 cells is a survival factor for eosinophils, as well as a chemotactic factor. So, eosinophils play a central role in high T2 inflammation. Also, on the right side, you can see how non-allergic, non-atopic signals can actually utilize a very similar pathway. Here, viruses, pollutants, tobacco smoke, can induce injury of epithelium to secrete TSLP, IL-33, and IL-25. Now, these alarmins that are induced by viruses and pollutants can directly affect ILC2 subsets, T cell subsets, to again secrete IL-13 and IL-5. IL-5 again, very important, and as a beacon to bring eosinophils

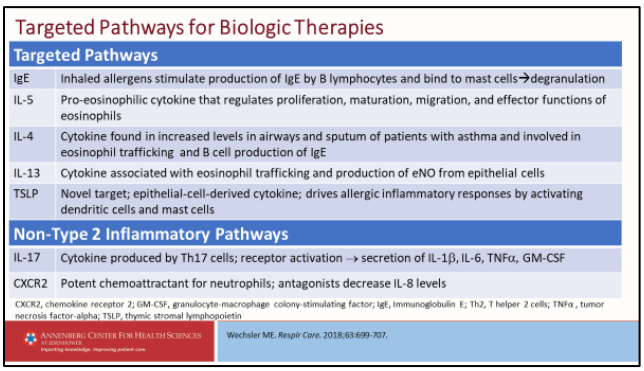
into the submucosa. IL-13, by the way, also modulates mucus gland hypertrophy and hyperplasia, as demonstrated here.

So, in this cartoon, rather complex, my apologies, but it's not simple. There are atopic allergen-driven T2 ultimately affecting eosinophils, as well as non-allergic stimuli that can affect alarmins that then modulate ILC2 secretion of similar cytokines. Again, IL-5 mediated is inducing eosinophil trafficking, as well as survival.

Now, the pathophysiology of T2-low asthma is far less explored. Here, we're showing the alarmins again play a central role, but in this case, the subset of T cells are the Th17 cells. Th17 cells can modulate neutrophil trafficking and function and also modulate Th1 T cell subsets. IL-8 is the chemotactic factor here. But again, you can see that the low T2 asthma is really relatively unexplored compared to the high T2 asthma.



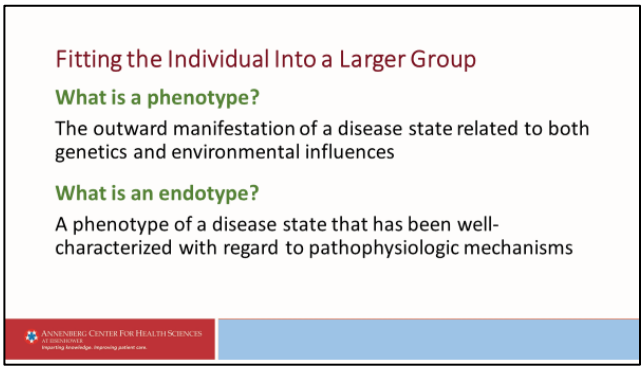
Now, there are targeted pathways that we have therapeutics [for] and these therapeutics target IgE. This is again IgE being secreted. There are monoclonal antibodies that block the IgE, preventing it from binding to the FC-Epsilon high affinity receptors. IL-5 is an eosinophil cytokine, as I mentioned before, chemotactic factor, as well as a survival factor for eosinophils, very important. Removal of IL-5 with monoclonal antibodies induces apoptosis of the eosinophils. Now, IL-4 and IL-13 actually activate receptors that are heterodimers, but have a common IL-4-alpha-receptor dimer. And that, when blocked, mitigates the effects of IL-4 and IL-13. Now, 4 and 13 are important in generating exhaled nitric oxide (eNO) but also in eosinophil trafficking downstream. And it can also play a role in switching phenotypes of B cells to secreting IgE cells. There is a monoclonal antibody that targets the IL-4 alpha-receptor and that would block the IL-4 and IL-13 pathways. Now, TSLP is a relatively novel alarmin that's been identified to play a role in asthma, and there is a biologic being developed here. As I mentioned, this is pretty upstream. From eosinophils or from T cell subset activation. And TSLP monoclonals may be available in our quiver in the future. Now the non-type 2 pathways mediated by IL-17 or CXCR2, that would be the IL-8 receptor antagonists, would have an effect on neutrophils but are far less developed. And we don't have them in the foreseeable future as therapeutics in severe asthma.



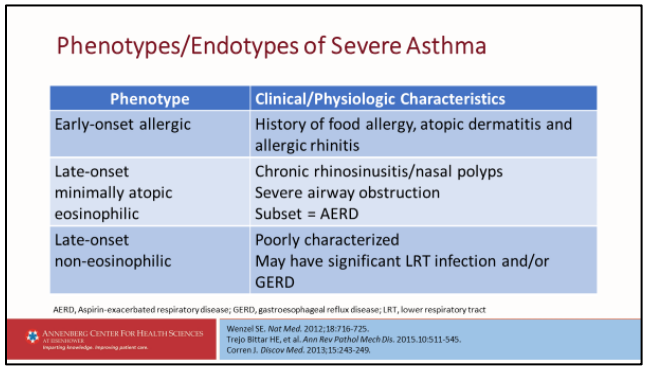
Case #2: A 63-year-old woman is being seen following a self-managed exacerbation that began about 3 days ago. She completed a 5-day course of prednisone, a pretty hefty dose, 40 mg a day, according to her action plan. Now, prior to the exacerbation, her standard of care was medium-dose inhaled corticosteroid (ICS) and long-acting beta-agonist (LABA). But she reported her asthma was not well controlled over the past 6-9 months. Review of pharmacy records showed good adherence with controllers, but increasing frequency of short-acting beta-agonists or rescue therapy. She does demonstrate good inhaler technique and no new risk factors for exacerbation. For example, hasn't had a new cat or other triggers that could be identified.

Clearly, this woman, older than an adolescent or young child, is having exacerbations requiring oral corticosteroids. So again, a severe asthma patient.

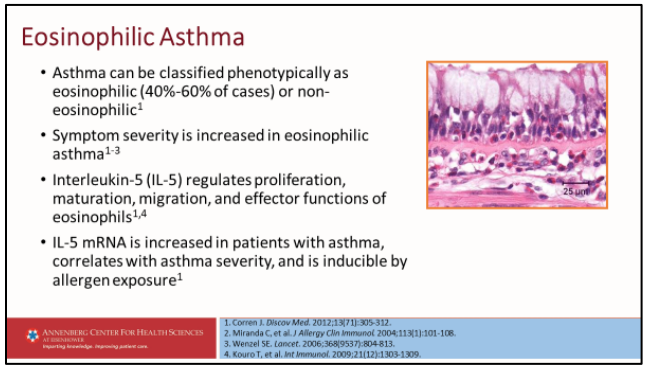
So, how do we fit case #1 and case #2 into the broader schema? And within what context? Well, fitting an individual into margin groups really requires familiarity with 2 terms: phenotype and endotype. So, what is a phenotype? Phenotype are outward manifestations of a disease state. Let's call them attributes. Attributes of the patient related to both genetics and the environmental influences. But what is endotype? Endotype is a phenotype of a disease state, well characterized by a specific molecular mechanism causing the asthma. Now, endotype implies mechanism. Phenotype really refers to descriptors or attributes. So, they're fundamentally different. We want to treat the molecular mechanism because if we take out the molecular mechanism, the attributes of the disease go away.



So, what are phenotypes and endotypes in severe asthma? In this slide, we really highlight phenotypes, early-onset allergic, late-onset minimally atopic eosinophilic. And you can see the attributes of the phenotype. For the early-onset allergic patient, many children manifest this, they could have food allergies, atopic dermatitis, allergic rhinitis. The late-onset minimally atopic eosinophilic patient is the older patient, like case #2, who has chronic rhinosinusitis, nasal polyps, and has severe airflow obstruction that may not be completely reversible. And a subset of these patients actually has aspirin-exacerbated respiratory disease. The so-called Samter's Triad: nasal polyps, aspirin sensitivity, and severe asthma. Late onset non-eosinophilic is a group of patients that are really quite poorly characterized. They may have significant chronic infection and/or GERD, gastroesophageal reflux disease. So, that is phenotypes.



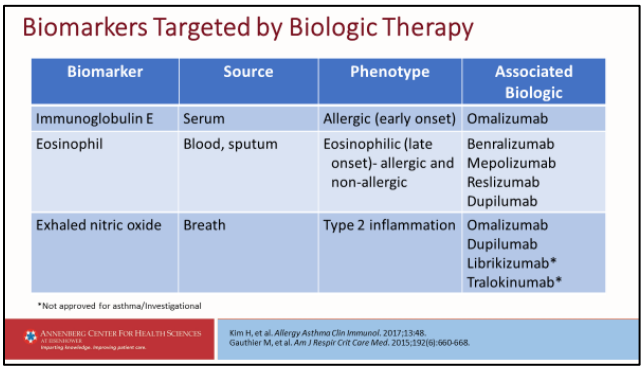
If we think about endotypes, we can start to think about maybe an IL-5-driven eosinophilic asthma. Here, in this slide, we really highlight some of the important aspects you need to consider when considering the eosinophilic asthma. It occurs in about 40% to 60% of cases with asthma and we're defining this, by the way, as greater than or equal to 150/µL eosinophils in the peripheral blood. Symptom severity is increased with greater eosinophil counts in the periphery. IL-5 is a major player. Remember what I mentioned? It is a survival factor and a chemotactic factor. Without IL-5, eosinophils will apoptose or die. IL-5 mRNA is increased in asthma and clearly occurs, and it relates to asthma severity and disease severity.



So, what are the biomarkers you need to measure in every patient in the assessment of their severity of disease? In this table, IgE is very important. We need to know whether the patient is atopic, non-atopic. Now, it's not just total IgE. That doesn't tell us as much as we need to know. What we really need to know is specific IgE. Are you allergic to a specific factor? I typically will use radioallergosorbent (RAST) testing. Many of my colleagues or allergists will use skin testing. Again, here the phenotype is allergic, often early onset with a long history of asthma, and the associated biologic to countermand the biomarkers, omalizumab. Omalizumab will target the soluble IgE. What about the eosinophil? Well, the eosinophil and the one we use as a surrogate is the blood eosinophil. Now, this is going to be found in older patients. Later onset, typically can be allergic or non-allergic, and we have a host of therapies in this space. Three anti-IL-5s, benralizumab, mepolizumab, reslizumab. Now, these have slightly different mechanisms of action. Reslizumab and mepolizumab will bind soluble IL-5, whereas benralizumab binds the receptor to which IL-5 binds. Now, those receptors, by the way, are found predominantly on the eosinophils and basophils. Also, unique to benralizumab, is that it will activate a pathway using natural killer (NK) cells to actually kill the eosinophil. All the anti-IL-5s are very effective in nearly obliterating, and in the case of benralizumab, absolutely obliterating, eosinophil counts.

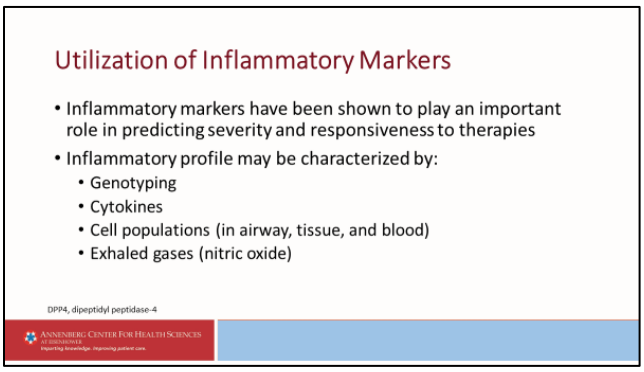
Now, dupilumab has a different mechanism of action from the IL-5s, and this blocks the IL-4-alpha-receptor. And even though it blocks the IL-4/IL-13 signal, it also has been shown to be effective in eosinophilic asthma. Exhaled nitric oxide (eNO) is the other test that I measure. So just to recap, specific IgE, total IgE to determine atopic, non-atopic, blood eosinophil counts greater than 150/μL puts the patient in an eosinophilic endotype. Exhaled NO allows us to get a perception of IL-4 and IL-13 mediated inflammation.

In this case, we know that dupilumab is quite effective. Omalizumab also has shown efficacy when exhaled NO is high. So, the ones you need to know about for exhaled NO is really dupilumab, whereas the anti-IL-5s are really not effective in lowering eNO counts.



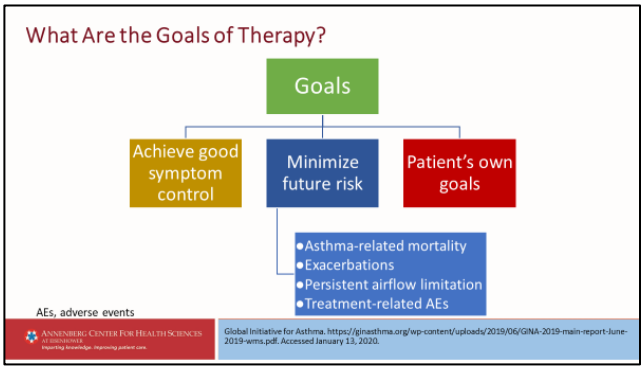
What about the utilization of inflammatory markers? Well, these markers—as I mentioned—the biomarkers, are really important. Other inflammatory markers have been research tools, but haven't seen clinical utility, as of yet, in predicting severity of disease and responsiveness to therapies.

Inflammatory profiles can be measured by genotyping cytokine cell populations and tissue and sputum exhaled gases. There are many other biomarkers currently under investigation, but none have been approved for the characterization of the severity of asthma.

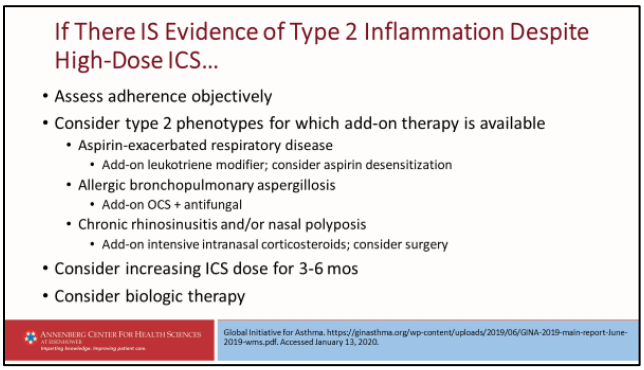


Case #3: A 34-year-old woman with long-standing asthma is seen in referral by her primary care physician. Asthma has been well controlled on high-

dose ICS, long-acting beta-agonist, and long-acting antimuscarinic agents. Periodic attempts to step down, though, showed and revealed worsening of symptoms. Reports increasing difficulty with yard work and is considering hiring a landscaper. Now, she has good adherence and good inhaler technique that was verified. She has heard about new medicines and wonders if any one of these are good for her. So again, long-standing asthma, on the lower end of middle age, maxed out on inhaler therapy, and we don't know about any exacerbations.



Is there evidence of type 2 inflammation despite high dose ICS? But you've maxed out her ICS, LABA therapy, and one would say, "Okay, I've covered that base, but there is steroid insensitivity." First, second, and third most important things you need to do, is assess adherence objectively. Then consider the type 2 phenotypes that we mentioned. Does she have aspirin-exacerbated respiratory disease? You may want to consider aspirin desensitization or leukotriene modifier. Does she have ABPA, that is, allergic bronchopulmonary aspergillosis? If that's the case, [you] may consider an antifungal or low-dose oral corticosteroid. What if she had chronic rhinosinusitis and nasal polyps? Add on intensive intranasal corticosteroids or consider surgery. And yet today, we do have some monoclonals that have been approved for nasal polyposis. Consider increasing the inhaled corticosteroid dose for 3-6 months, or move on to a biologic. And at this point, frankly, in this case, I would opt to move on to a biologic because I'm very concerned about oral corticosteroid burden. That is, the side effects associated with oral corticosteroids.



Need to consider shared decision-making though. We just talked about 5 biologics, in this space, of severe asthma. All of them are subcutaneous, but many can be given at home. One, reslizumab can be given intravenously (IV). So, we need to understand what are the goals the patient seeks, as well as what's the therapy, the precision and personalized approach that will work for this patient to enhance adherence. Seek the patient's participation. Give her the data, that you could take some of these drugs every 2 weeks, you could take some of these drugs monthly for 3 [months] and then every other month. Some come by IV. Many can be given at home. Help your patient explore and compare the treatment options.

Is there the perfect therapy or are there comparable therapies? And if the patient is engaged in the decision-making, you'll enhance adherence. Assess the patient's values and preferences, reach a decision together with the patient as a shared approach, and evaluate the patient's decision, making sure that there are finite goals and milestones that you will read back to the patient.

BIOLOGICS IN SEVERE ASTHMA:
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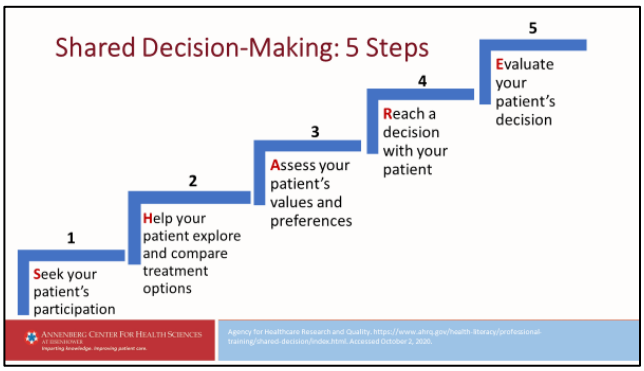
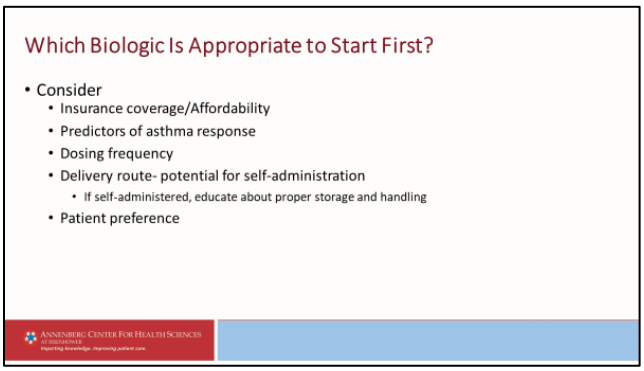




Case #4: Now, much different patient, 9-year-old male being seen with his mother in referral from the primary care provider due to increasing symptoms. Increasing ICS has yielded minimal improvement. And the current therapy is a medium-dose ICS, long-acting beta-agonist. Which biologic would be appropriate if he had *in vitro* reactivity to a perennial aeroallergen? Now, remember the nature of the child, the age, puts the child likely in the atopic category and has sensitivity to perennial aeroallergen. Well, in that case, maybe omalizumab would be the ideal drug.

Now, which biologic would be appropriate if the blood eosinophil count was 180/μL, slightly over 150/μL? But if we look at the age, and consider the atopic nature, we might still choose a drug that would target IgE.

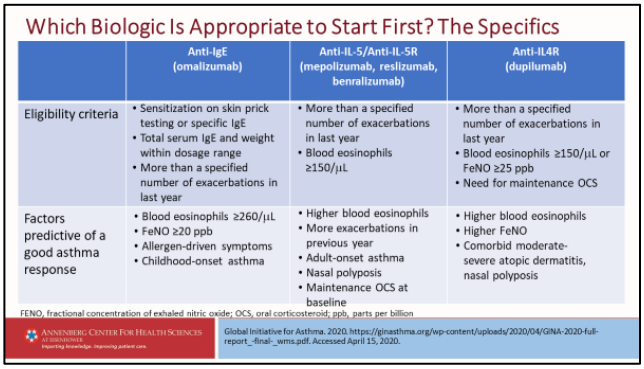
So which biologic is appropriate to start first? Very important, consider insurance coverage and affordability. If the patient can't afford the medicines, has poor access to the drugs, not likely to be adherent. What are the predictors of an asthma response in the case of eosinophils in the periphery? The higher the eosinophil count, the more likely you are to respond to IL-5. Dosing frequency twice a month, monthly, every 8 weeks. We have choices. And the delivery route, potential for self-administration, home administration. Need to be sure that the patient has the capability of storing and handling the drug appropriately, and ultimately, you've got to involve the patient. What do they want? Do they want the ability to self-dose?

So, which biologic is appropriate to start first, and some of the specificities? Well, here we have anti-IgE that's only omalizumab, we have anti-IL-4 soluble, that's going to be mepolizumab and reslizumab, where benralizumab is the IL-5 receptor. And dupilumab is the only IL-4-alpha-receptor antagonist. The eligibility criteria are shown here. Again, for anti-IgE, total IgE, and weight will determine the dose. But the specificity of the response is going to be driven, in part, by the number of aeroallergens or sensitivities specific IgEs.

For the anti-IL-5, it's all about the eosinophil in the periphery, higher, more likely to respond.

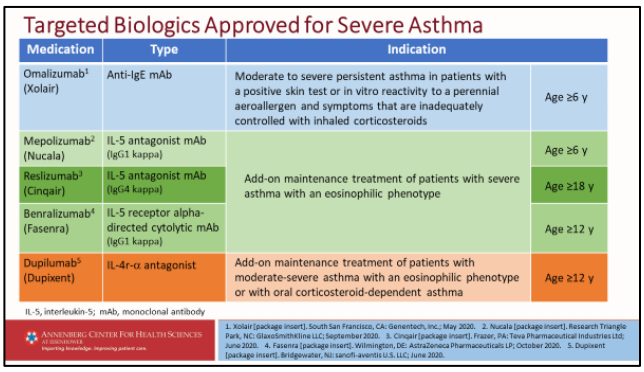
Again, what predicts best response? High eosinophils, more exacerbations, adults, nasal polyposis, and maintenance oral corticosteroid. For those getting the anti-IL-4-alpha here, I think fractional concentration of exhaled nitric oxide (FeNO) is a very good predictor of response and high yields. The combination of those 2 adds opportunity. We know the higher the blood eosinophils, the higher the FeNO, and comorbidity predicts response. So, there's subtleties—and maybe not so subtle differences—in choosing biologics. We have the opportunity to be precise in our prescribing of biologics to manage severe asthma.

BIOLOGICS IN SEVERE ASTHMA: OPTIMIZING THERAPEUTIC SELECTION AND PATIENT OUTCOMES



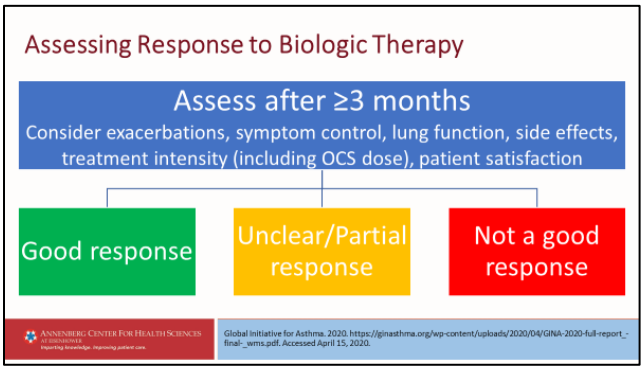
Now, the target biologics for severe asthma are listed in this table, omalizumab (Xolair), mepolizumab (Nucala), reslizumab (Cinqair), benralizumab (Fasenra) and dupilumab (Dupixent). That is the anti-IL-4-alpha-receptor antagonist. So, the indications, we've already covered many of these indications, you can see them here, all are going to be Global Initiative for Asthma (GINA) 4 or 5, moderate to severe persistent asthma.

Many of these drugs have shown efficacy in oral corticosteroid bearing. Now, there are very selective age differences. In the case of mepolizumab and omalizumab age greater than or equal to 6 years is appropriate. For the IV formulation of reslizumab, that's for age greater than or equal to 18 years, or age greater than or equal to 12 years for benralizumab and dupilumab.

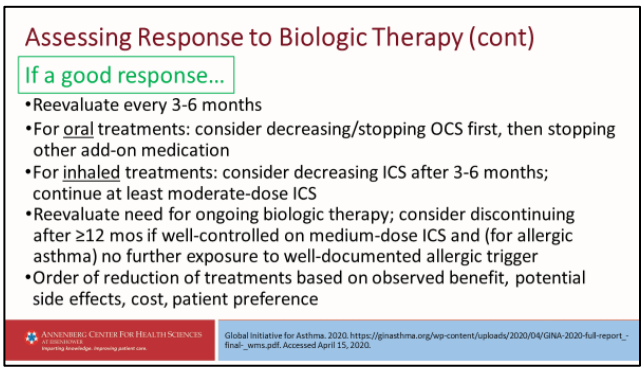


Case #5: A 61-year-old woman is newly diagnosed with severe eosinophilic asthma. Has missed work 7 days over the past 10 months. Currently on high-dose ICS, long-acting beta-agonist. And the decision was made to use an anti-IL-5 biologic. Education written action plan was provided. Now, how will you evaluate success?

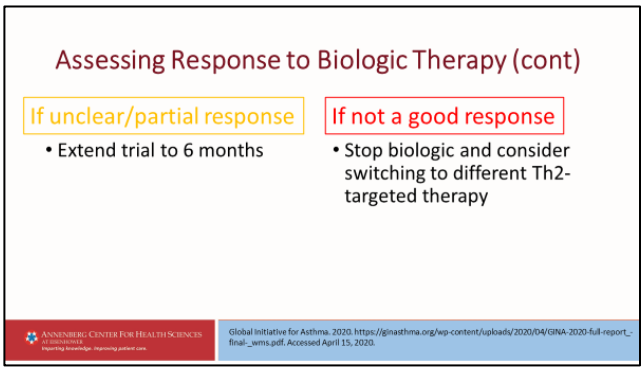
First and foremost, after starting anti-IL-5, I am going to measure the eosinophil count in the periphery. I want to know the target has been engaged. Doesn't tell me whether the patient's going to be better or not. But it will tell me if I've obliterated the eosinophils. If the patient started with 400/μL, after a month of therapy I would hope to see this less than 100/μL, optimally zero. That would tell me that I've engaged the target. Now, the fancy term for that is a pharmacodynamic biomarker.



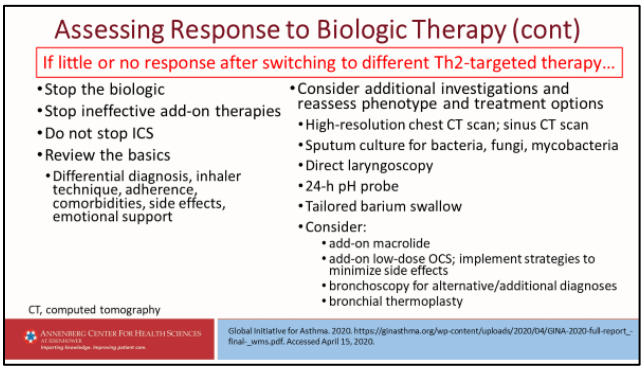
If a good response, reevaluate every 3-6 months. For oral treatments, considering first and foremost, tapering or eliminating oral corticosteroids for inhaled therapy. I would also consider decreasing ICS. Now you've got to be cautious about too quickly tapering either inhaled or oral steroids for fear of inducing adrenal insufficiency. You still need to reevaluate. Even if you're tapering the current therapies, you need to be sure that the patient has maintained control. Order of reduction of treatments is based on the observed benefit, potential side effects, cost, and adherence, all play important roles.



What if it's an unclear or partial response? Well, maybe you need a little longer, so I would go for 6 months. But if not a good response in 3 or greater months, then I'm stopping and considering switching. I want to kill a drug quickly and move on to the next choice. We have options. No reason to maintain a patient on a drug that is not meeting the goals or the benefits. If little or no response after switching to different Th2 therapies, then I would consider stopping the biologic.



These medications are expensive. You do not want to stop the ICS. Review the basics, make sure the patient has asthma. Make sure there's some component of reversible airflow obstruction. Look for comorbidities, nasal polyposis, GERD. Consider other investigations. I typically will do a high-resolution CT scan or sinus CT to assess polyposis or alternative diagnoses in the lungs. May consider a 24-hour pH probe. And then, if all that has been done, still you've come up with a diagnosis of severe asthma, difficult to treat non-T2, unresponsive to biologics. Then I would consider a macrolide antibiotic, Monday, Wednesday, Friday, 250 mg. And the reason is, this is an anti-neutrophil drug, not an anti-infective. I also would consider this group of patients for bronchial thermoplasty.



Case #6: An 18-year-old male with a 4-year history of asthma, is being seen by a pulmonologist, with worsening asthma control. Evaluation reveals severe, non-allergic eosinophilic asthma. During the discussion, he expresses concern about the long-term damage to his lungs and wonders if new medicines may reverse it. Again, the focus here, younger patient, 4-year history of asthma, has eosinophilic asthma, and poor control.

There's no data regarding the impact of biologic therapy and lung damage or the consequences in preventing irreversible airflow research. That's very important to get across. Everyone wants to prevent airway remodeling, aka, irreversible airflow obstruction. To date, no evidence, no drug is available to show that we can prevent the progression of irreversible airflow obstruction.

Summary: So, I want to summarize. We just took a whirlwind tour through 6 cases, the pathophysiology biomarkers, the utility of biomarkers, and determining precision approaches to biologics. But I do want to leave you with a couple of points. Asthma is a heterogeneous disease, no doubt about it. Patients respond in a heterogeneous manner. So even with the heterogeneity of the disease process, each patient actually responds uniquely to a therapy. Improved understanding of asthma pathophysiology has led to the development of exciting biologics that

target specific phenotypes utilizing the molecular mechanism and concept of endotypes.

Inflammatory markers have been shown to play an important role in predicting asthma severity and responsiveness to biologics. Differences among available biologics provide greater opportunity to tailor therapy, and to use it in a precise manner using shared decision-making, giving the patient options, and as a partner, working towards improvement of asthma control. Treatment response should be evaluated every 3 months. If good response, then continue, but reassess. If incomplete, you may extend it for 6 months.

If no hint of success, then switch the biologic. Unfortunately, there's no data regarding the effect of biologic therapy on airway damage; and airway damage is really the phenotype of irreversible airflow obstruction. So, I hope this talk using case-based approaches has given you a glimpse of how we currently manage severe and uncontrolled asthma. It's an exciting time. We've never had so many arrows in our quiver to treat this disease process. And it's an exciting time for our patients, who we feel can be greatly impacted to improve their quality of life and functional status.