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## Severe Asthma and Related Eosinophilic Diseases: The Role of IL-5 in Diagnosis and Treatment

Dr. Wang:

Hi, I'm Dr. Eileen Wang, an allergist/immunologist and together with my pulmonary colleague, Dr. Ron Balkissoon, we will be discussing the role of IL-5 in severe asthma and other related eosinophilic diseases. We both work at National Jewish Health in Denver, Colorado. Dr. Balkissoon, thank you so much for joining us today.

Dr. Balkissoon:

It's a pleasure, Eileen.

Dr. Wang:

In this chapter, we will be discussing the epidemiology and pathophysiology of severe asthma, relevant biomarkers and endotypes and some associated eosinophilic diseases and when to refer to a specialist. In terms of the epidemiology of severe asthma according to the 2014 CDC National Health Interview Survey Data, 7.4% of the adult population in the United States carry a diagnosis of asthma. It was estimated that 5 to 15% of asthmatics have severe asthma. However, a precise figure is difficult to determine given the heterogeneity of the disease, lack of clear classification guidelines, and incomplete reporting. It is important to identify the subgroup of asthmatics because of their high healthcare utilization and increased risk of asthma, morbidity, and mortality. This group accounts for 50% of healthcare utilization related to asthma and is at increased risk of asthma-related death. When managing severe asthma, it's important to distinguish between difficult to treat asthma and refractory asthma. Difficult to treat asthma includes those with inadequate response to treatment secondary to poor adherence, poor medication technique and/or uncontrolled aggravating or masquerading comorbidities. In contrast, refractory asthma, as defined by the 2014 ERS/ATS guidelines, encompasses disease that remains uncontrolled despite adjusting comorbidities, excluding alternative diagnoses, removing triggers, and checking adherence. This is also despite high intensity treatment or requiring systemic corticosteroids to maintain control. Regarding asthma pathophysiology, while there's frequently overlap and interplay between elements of smooth muscle dysfunction, airway inflammation, and airway remodeling, asthmatics can have different predominant pathophysiologic mechanisms at play – that seemingly can flare independently of one another. As an example, largely rising from studies of biologic therapies, are conceptualization of a direct concordance between FEV1 and systemic corticosteroid requiring exacerbations may not be completely accurate. A study of an anti-IL-5 drug found that it worked best in those with less than 50 mL change in FEV1 after receiving a short-acting beta-agonist rather than those with greater bronchodilator reversibility. Thus, the underpinnings of asthma exacerbations may differ from those pathways driving bronchial tone. Specifically, anti-IL-5 work best in those that had symptoms and airflow limitation resulting from corticosteroid responsive inflammation rather than smooth muscle contraction. There have also been other studies in asthmatics that found weak relationships between FEV1 and airway inflammation along with poor correlation between airway hyperresponsiveness to methacholine, and airway eosinophilic inflammation. Now, let's take a look at the animation on the mechanisms of inflammation. It is increasingly evident that severe asthma is not a single disease as evidenced by the variety of clinical presentations, physiological characteristics, and outcomes. To better understand this heterogeneity, the concept of asthma endotyping have emerged. Endotyping aims to identify mechanistic pathways in asthma. These entail type 2 or type 2-high or non-type 2 endotypes. For this discussion, we'll be focusing on the type 2 asthma endotype. To understand type 2 asthma and its mechanistic pathways, we focus on innate lymphoid cells, T-helper 2 cells, eosinophils, IgE, and associated cytokines. Asthma originates from complex interactions between genetic factors and environmental agents, such as air

allergens and respiratory viruses. Stimuli, such as viruses, allergens, and air pollution, cause airway epithelial cells to secrete thymic stromal lymphopoietin or TSLP, IL-25, and IL-33. This leads to dendritic cell activation. Commitment to the Th2 lineage is driven by IL-4. TSLP, IL-25, and IL-33 also activate group 2 innate lymphoid cells or ILC2 cells. ILC2 and Th2 cells lead to release of IL-5, IL-4, and IL-13. IL-5 induces eosinophil maturation and survival. IL-4 and IL-13 drive immunoglobulin class switching and promote B cell synthesis of immunoglobulin E or IgE antibodies. Antigen-induced IgE bridging promotes mass cell degranulation and the subsequent release of preformed granule-associated mediators, which include histamine, tryptase, kinase, and heparin. In addition, newly formed eicosanoids, such as cysteinyl leukotrienes C4 and D4, and prostaglandin D2 are secreted, as well as several different cytokines, chemokines, and growth factors. Eosinophils release toxic granule proteins, reactive oxygen species, leukotrienes, growth factors, and cytokines. These all lead to smooth muscle cell contraction with hyperresponsiveness and hyperplasia. Mucus hypersecretion along with impaired mucus clearance increase the eosinophils in the airway lumen and airway remodeling with fibroblast activation and proliferation leading to fibrosis and collagen deposition. This cascade results in inflamed, hyperresponsive, and narrow airways with constricted muscles and increased mucus that results in the coughing, wheezing, dyspnea, and chest tightness asthmatics experience. It is increasingly evident that severe asthma is not a single disease, as evidenced by a variety of clinical presentations, physiological characteristics, and outcomes. As a result, the traditional approach to therapy has evolved into a more personalized and tailored approach. To better understand this heterogeneity, the concepts of asthma phenotyping and endotyping have emerged. Phenotyping integrates observable, biological, clinical, and physiological features with the goal to improve therapy. Ultimately, the strategy has evolved into asthma endotypes, which define mechanistic pathways at a cellular and molecular level. A biomarker is defined as a characteristic that is objectively measured and serves as an indicator of biological processes, pathogenic processes, or pharmacologic responses to an intervention. In asthma, these include: total serum IgE, peripheral eosinophils, sputum inflammatory cells, and also exhaled nitric oxide. Now, we will look at animation on the clinical phenotype and endotype of severe asthma.

Dr. Balkissoon:

Looking at this figure, we can identify common biomarkers currently used in clinical practice including eosinophils, IgE, and neutrophils. Exhaled nitric oxide is produced by airway epithelial cells and eosinophils and macrophages and primarily reflects IL-4 and IL-13 activity. Sputum neutrophils are a surrogate marker of non-T2 inflammation. Eosinophilic airway inflammation accounts for approximately 40 to 60% of patients with severe asthma. Sputum eosinophils greater than 3% have been considered the – to be indicative of significant eosinophilic inflammation. Unfortunately, it can be somewhat difficult to collect adequate sputum samples for processing, but there have been fairly good correlations found between sputum and blood eosinophil counts and cutoff values typically between 150 to 400 eosinophils per microliter have been used to predict response to anti-IL-5 antagonist. Serum total IgE and specific IgE have been good markers for identifying the environmental atopy and phenol concentrations are greater than 50 parts per billion, greater than 30 parts per billion in children, are indicative of steroid responsiveness. Non-T2-high asthma is officially defined by the absence of T2 biomarkers. It can be characterized by sputum neutrophil counts that are greater than 40 to 60%. Whereas, a pauci granulocytic picture presents as normal sputum levels of both eosinophils and neutrophils. Clinically, it's identified by a lack of response to corticosteroid therapy. Common clinical phenotypes associated with these various endotypes include atopic, late onset, and aspirin-exacerbated respiratory disease, asthma with T2-high, a mixed picture with high neutrophils and high eosinophils has been associated with smoking, infections, and aspiration, and a pauci granulocytic picture can be seen in the nonatopic group and neutrophilic has been identified in the obese female, infection, irritants, aspiration, and altered microbiome groups. The T2-high endotype will be responsive to the typical biologics currently available, such as anti-IgE, anti-IL-5, and anti-IL-4, IL-13 medications. The mixed group may respond to these biologics, but may require additional therapy, such as macrolide antibiotics. The neutrophilic group may be possible responders to macrolides, and the pauci granulocytic group may be good candidates for consideration in bronchial thermoplasty.

Dr. Wang:

The differential diagnosis for peripheral eosinophilia is broad and includes atopic diseases, eosinophilic gastrointestinal diseases, paracytic infections, certain cancers, adrenal insufficiency among others. Ones we will highlight are hypereosinophilic syndrome, chronic sinusitis with nasal polyposis, and eosinophilic granulomatosis polyangiitis. Diagnostic evaluation will be discussed in Chapter 2 by Dr. Balkissoon, but we will highlight clinical features of these three. Chronic sinusitis with nasal polyposis is a disease frequently associated with peripheral eosinophilia and also is an important comorbidity that can complicate asthma management and contribute to poor control and increased exacerbations. Typical symptoms include nasal or sinus congestion or fullness, anosmia, or hyposmia. There is a 2:1 male to female ratio and incidence increases with age with a peak around 45 to 65 years. Polyps originate in the sinuses, appear to be sac-like, and contains a thickened basement membrane, edematous and fibrotic stroma, and increased inflammatory cells to include eosinophils and mass cells. There are two primary types of nasal polyps, ethmoidal and antrochoanal. Ethmoidal polyps develop from the ethmoid sinuses, whereas antrochoanal polyps, which comprise only 4 to 6% of polyps, arise in the maxillary sinuses. Eosinophilic granulomatosis polyangiitis or EGPA is a systemic small and medium vessel necrotizing vasculitis characterized by extravascular granulomas, peripheral eosinophilia, and eosinophilic inflammation. EGPA can affect multiple organ systems. Clinical

manifestations of the lung include pulmonary vasculitis, pleural effusions, hilar lymphadenopathy, and cavitary lesions. In the heart, you can see acute or constrictive pericarditis, cardiac failure, and myocardial infarction. In the central nervous system, you can have mononeuritis complex. In the gastrointestinal tract, you can have eosinophilic gastroenteritis and polyarteritis nodosa. In the kidney, you can have focal segmental glomerulonephritis. In the musculoskeletal system, you can develop myalgia and joint pain. For the skin, there can be multiple manifestations to include purpura, macular or papular erythematous rash, urticaria, or even subcutaneous nodules. Hypereosinophilic syndrome is a disease associated with significantly elevated peripheral eosinophilia and organ involvements. In the respiratory tract, you can see pulmonary infiltrates, pleural effusions, asthma, sinus disease, cough, and recurrent infections. In the cardiovascular system, you can see cardiomyopathy, pericardial effusion, cardiac failure, myocarditis, and valvular disease. In the nervous system, you can see vertigo, paresthesias, change in mentation, aphasia, and visual changes. In the gastrointestinal tract, you can have abdominal pain, vomiting, and diarrhea. Constitutional symptoms include fever, weight loss, malaise, fatigue, night sweats, and flu-like symptoms. Rheumatologically, there can be myalgias, joint pain, and myositis. In the skin, there can be a broad range of clinical manifestations to include urticaria, angioedema, dermatitis, eosinophilic vasculitis, and bullous lesions. And lastly, hematologically, you can have deep venous thrombosis, anemia, and superficial thrombophlebitis. Type 2-high endotype asthmatics have been an important population of focus because of studies demonstrating worse asthma outcomes. Prior to development of biologics for this endotype, which will be discussed in Chapter 3, those with higher exhaled nitric oxide and/or peripheral eosinophilia compared to those without had worsened air flow obstruction, increased bronchial hyperresponsiveness, worsened asthma control, and increased frequency of asthma exacerbations. According to the Global Initiative for Asthma or GINA 2019 report, asthmatics with uncontrolled symptoms and/or exacerbations despite – studied – for treatment on at least a medium dose combination of inhaled corticosteroid and long-acting beta agonist, should be referred to a specialist for assessment of contributory factors, optimization of treatment, assessment of phenotypes and endotypes, and consideration of add-on treatments such as biologics. Also, consider referral to an asthma specialist if signs and symptoms are atypical. If there are problems with a differential diagnosis or if additional testing is indicated.

Dr. Wang:

For those who are just joining us, this is ReachMD. I'm Dr. Eileen Wang, and I have the pleasure of speaking with Dr. Ron Balkissoon on the topic of severe asthma and related eosinophilic diseases. Dr. Balkissoon will now discuss the clinical evaluation of severe asthmatics and how to differentiate other significant eosinophilic conditions.

Dr. Balkissoon:

In this section, we're going to look at the differential diagnosis of severe asthma and associated eosinophilic diseases. We're going to look at the clinical evaluation of severe asthma and then also look at differentiating it from other conditions, such as chronic rhinosinusitis and nasal polyposis, allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis and polyangiitis, also known as EGPA, and hypereosinophilic syndrome, which is also known as HES. When we look at the assessment of severe asthma, the first thing we want to do is be able to confirm the asthma diagnosis. This obviously involves looking at symptoms and reviewing the medications that the patient is on, as well as doing physiologic testing, such as pulmonary function test and methacholine challenge looking for bronchial hyperreactivity. Sometimes there are challenges in identifying patients who have asthma and bronchoscopy can actually be helpful in that particular patient population; not to mention looking for evidence of comorbid conditions that often complicate asthma. The next thing that we look at is asthma severity. And for that, we're really looking at the issues of whether or not the patient is on high-dose, medium-dose, or low-dose inhaled corticosteroids, and what other types of control or medicines they might be on including long-acting beta agonist, uh, theophylline, long-acting muscarinic antagonist, and even oral corticosteroids or have they actually been on prior biologics to the time that we're evaluating them? And then we need to look at optimizing inhaled therapy. This means looking at a patient's inhaler technique, as well as their adherence to their therapy. And this is when we try to make decisions about stepping up or stepping down therapy and also whether or not it's appropriate to refer them to a specialist, as was outlined by Dr. Wang. The next step is assessing the degree of control that the patient has in terms of their severe asthma. And for this, we focus on assessing the frequency that they've had exacerbations in the past 12 months. So if they've had two or more exacerbations that have required systemic steroids that have lasted for, at least, three days, or if they've had, at least, one hospitalization or ICU stay that required intubation, these are considered evidence that a patient has poor control. We've also used lung function because there's an implication that when a patient's FEV1 is less than 80%, this is a sign of individuals who have suboptimally controlled asthma. Also, we can use the asthma control test or the asthma control questionnaire, and as you can see, if – it – they're using the asthma control test, if the score is less than 20 or in the asthma control questionnaire, if the score is greater than 1.5, these are indications that a patient has poorly controlled asthma. Once we've assessed the level of control that a patient has, the next thing is to try to endotype and phenotype them with regard to their asthma. We use a variety of tools including such things as allergy testing, which can be measured in the skin and blood. We also look at the IgE level, exhaled nitric oxide level, and CBC and sputum eosinophils are extremely important. In some instances, we may even further try to endotype patients by using bronchoscopy. Essentially, we have two different significant endotypes. We have T2-high and

non-T2, uh, asthma. When we measure the blood eosinophil count, typically for T2-high asthma, it's greater than 150 and somewhere in the range of 150 to 400 eosinophils per microliter. We can also use sputum eosinophilia, and that's typically designated by sputum eosinophil count of greater than 3%, and we also look for increased IgE and specific IgE as well. The exhaled nitric oxide level can be measured and while 25 and less is considered to be normal, ENO of greater than 50 parts per billion, typically indicates an individual that should be responsive to, uh, oral and inhaled corticosteroids. For the non T2 endotype, this is typically evidenced by patients having more of a neutrophilic-type of inflammation or perhaps having no significant inflammatory infiltrate at all. We can measure sputum neutrophils, and these are typically in the 40 to 60% range in those who have non-T2 asthma or as I said, you may have pauci granulocytic where there are normal neutrophil levels and eosinophil levels found. Once we've phenotyped and endotyped patients with severe asthma, it is also important to look for comorbid conditions. These can often complicate asthma management, and this really falls into the paradigm of patients who have difficult to control asthma. The conditions that we typically look for include such things as gastroesophageal reflux disease, and a number of these patients may actually also aspirate, and this is often picked up on CT scanning. A number of them may also develop dysbiosis or chronic infections. We know that patients who are on high-dose inhaled corticosteroids are at a greater risk of developing alterations of the microbiome. Obesity has been associated with more difficult to control asthma. We also know that there are a subset of asthma patients who also have concomitant chronic obstructive pulmonary disease. And in addition to that, paradoxical vocal fold motion disorder or what now is called inducible laryngeal obstruction, is an important thing to rule out, as well as bronchiolitis, and we see a number of patients who have tracheobronchomalacia, who also have severe asthma. All of these are important comorbid conditions that we need to rule out that may be making the patient's asthma more difficult to control and the underlying asthma may actually be reasonably well controlled. When looking for comorbid conditions that – there are different investigative modalities that can be extremely helpful. CT scanning can be extraordinarily helpful in identifying patients who have hiatal hernias and gastroesophageal reflux disease and possibly consequent aspiration. Bronchoscopy is extremely useful in identifying patients who have tracheobronchomalacia and laryngoscopy following methacholine challenge can also identify those patients who have inducible laryngeal obstruction or what we used to call vocal cord dysfunction. In addition to trying ruling out significant comorbid conditions, it's also extremely important to rule out other eosinophilic conditions. These include such things as chronic rhinosinusitis with nasal polyposis, allergic bronchopulmonary mycosis or aspergillosis, eosinophilic granulomatosis with polyangiitis or EGPA, and hypereosinophilic syndrome, which is also known as HES. When evaluating these patients for eosinophilic lung diseases, it's extremely important to understand that a history and physical will be invaluable. Most of the conditions that I mentioned are often associated with asthma, so understanding if they do have a significant asthma history, it's important. In addition to that, a travel history will be extremely helpful, particularly, when you're worried about the possibilities of them having underlying paracytic infections; and if they have multiorgan involvement, which can be gained by taking a good history and physical, that raises the questions of indeed whether they might have an eosinophilic vasculitis, such as EGPA or have hypereosinophilic syndrome. With that in mind, there is a broad array of tests that we need to include and that obviously involves looking at CBC eosinophil counts, but we're also going to want to look at ANCA, MPO, and PR3, as well as allergic bronchopulmonary mycosis screening and urinalysis is extremely important as well, as the eosinophilic vasculitis can often involve kidneys. In addition to that, obviously doing stool and serological studies for parasites is extremely important, and ultimately, if you're worried about a patient who might have hypereosinophilic syndrome, then bone marrow biopsy and karyotyping is extremely important in characterizing these patients. In addition, on pulmonary function tests, we gain information as to whether or not patients have restrictive patterns, which are often associated with the eosinophilic pneumonias, whereas the obstructive pattern is more often seen in patients who obviously have asthma, allergic bronchopulmonary mycosis and EGPA. CT scan can be awfully helpful in identifying opacities or infiltrates, which are often seen in HES and EGPA, and echocardiogram is important because a number of these patients can have cardiac manifestations that can be appreciated in an echocardiogram. As far as bronchoscopy goes, some of the patients who have EGPA can be diagnosed by bronchoscopy, but this may generally require some type of surgical biopsy. When evaluating patients for allergic bronchopulmonary aspergillosis or mycosis, the clinical features which are helpful are history of asthma or cystic fibrosis, as most patients who have this will have one or the other. Also, looking for signs of systemic and airway eosinophilia is important. So on lavage or sputum or indeed in the blood, detecting high eosinophile counts is important. They will often have elevated IgE level, but this can often be affected by how much prednisone they've been on in the past. Lung infiltration and bronchiectasis are key signs that one will see on CT scanning in addition to mucoid impaction and lung fibrosis. When looking at ABPM or ABPA, the diagnostic criteria for this are patients who do have evidence of a history of asthma or CF. In addition to that, they'll have positive skin prick testing for aspergillosis or other molds, and their specific IgE will typically be greater than 35 kilounits per liter. IgEs are typically greater than 1000 for many of these patients, but as I said, if they had been on prednisone, the IgE can be lower than that. And they should have, at least, two of the following: they should have precipitating antibodies to aspergillosis fumigatus or other fungi, and they should also show radiographic signs of pulmonary opacities, which is consistent with ABPA, and the total eosinophil count should typically be 500 in a steroid naïve patient. When considering the pathogenesis of EGPA, one needs to appreciate the fact that it follows the Th2 pathways, but also there are other important pathways that seem to lead to tissue damage and vasculitis. Allergens that are processed by dendritic cells lead to differentiation of



undifferentiated Th0 cells to Th2 cells, as well as Th1 and Th17 cells. The Th1 and Th17 cells will cause the release of such things as IL-2, interferon gamma and IL-17 that leads to a granulomatous vasculitis and tissue damage. On the other hand, the Th2 cells will lead to the evolution of IL-4 and IL-13, as well as IL-5, this leads to eosinophilic activation and degranulation with release of such things as major basic protein and eosinophilic cationic protein, and these also will lead to significant tissue damage. When evaluating patients for EGPA, we understand that it's an eosinophilic vasculitis, and many of these patients will have multisystem involvement. They go through a prodrome and a secondary phase where they can have high in the blood and tissue, and then there's the third phase, which is a life threatening vasculitis. The testing that's important for this includes looking at the CT scan of the chest, as well as looking at peripheral blood eosinophilic counts, which are typically greater than 1,500, but can be as high as 5,000 to 9,000. ANCA testing is actually not that sensitive. Only about 30 to 60% of the patients who have EGPA will have a positive ANCA and only 70 to 75% of those will have a p-ANCA and the c-ANCA is not that common. Also, we'll look at surgical lung biopsy for many of these patients to make the diagnosis, and the typical sites include such things as the skin, kidney, and the lung, and less commonly, peripheral nerves. Urinalysis and echocardiogram is also extremely important. In terms of diagnostic criteria according to the American College of Rheumatology, patients should have four of the following six criteria; that includes a history of asthma, at least, 10% eosinophils on differential leucocyte count, and evidence for migratory or transient lung opacities. Also, they should have signs of a mononeuropathy or polyneuropathy, paranasal sinus abnormalities, or biopsies containing a blood vessel showing an accumulation of eosinophils in the extravascular areas. Hypereosinophilia is first considered in patients who have peripheral blood eosinophil counts of at least 1,500 cells per microliter on, at least, two separate occasions that are, at least, a month apart, and pathological confirmation of tissue hypereosinophilia can also be detected in the bone marrow where they have, at least, 20% of all nucleated cells being eosinophils and, otherwise, the pathologist may have the opinion that there's extensive eosinophilic infiltration. In addition to that, you can also look for marked deposition of eosinophilic granules and proteins in tissue. The signs of eosinophilic infiltration, degranulation, and mediator release in tissues leads to the multiorgan damage that is the hallmark of hypereosinophilic syndrome. So when we've identified individuals who have high eosinophil counts that are greater than 1,500 and we're considering hypereosinophilic syndrome, it is important to take a good history and physical, which will help to rule out secondary causes, such as parasites, allergic conditions, other pulmonary conditions, or connective tissue disorders. If these are found, these would be considered reactive eosinophilia. In the absence of these secondary causes, one would go forward and do the gene mutation study. If that's positive, it suggests that they have a myeloproliferative clonal eosinophilia, which is known as chronic eosinophilic leukemia. If it is negative, then there are a few other categories of hypereosinophilic syndrome that one needs to consider. Perhaps the most significant is lymphocytic hypereosinophilic syndrome where there is an abnormal T-cell line that's associated with HES, and this is also associated with an increased IL-5 production. The other categories are less well characterized including familial, for which there has been no mutation identified up to the current time. There is a clonal cytogenetic abnormality, which is called chronic eosinophilic leukemia, not otherwise specified, and then there remains idiopathic HES as well. What's important is with these two characterizations of the gene mutation, there is a medicine called imatinib, which may actually be very helpful in the myeloproliferative form and then lymphocytic HES recognizing that there – this is – there is this increased IL-5 production that anti-IL-5 agents may be amenable to treatment in the future, although this is not an improved indication at the current time. In lymphocytic HES, we know that there are abnormal T-cells that are associated with this condition, and there seems to be an increase in IL-5 production. This leads to the potential that anti-IL-5 agents may be useful for this condition, but at the current time, this is not an approved indication. When we find patients that may have these other conditions, there are a variety of specialists that may be very helpful. For chronic rhinosinusitis with nasal polyps, both ENT and allergists may be very helpful. Allergic bronchopulmonary mycosis patients may benefit from consultation with allergists or pulmonologists, and for EGPA, rheumatologists can be very helpful for ruling out vasculitis, and for hypereosinophilic syndrome, often hematologists are required to collect bone marrows and do karyotyping.

Dr. Wang:

Once again, for those who are just joining us, this is ReachMD. I'm Dr. Eileen Wang, and I'm here today with Dr. Ron Balkissoon discussing severe asthma and related eosinophilic diseases. Now that Dr. Balkissoon has discussed the clinical evaluation, we will both discuss the treatment selection for the spectrum of eosinophilic disease. Monitoring response to asthma therapeutics must include assessment of potential adverse effects. The incomplete efficacy of inhaled and systemic corticosteroids, along with significant adverse effects, are why biologic therapeutics are so greatly needed for severe asthmatics. Adverse effects to inhaled corticosteroids are more rare, but are likely secondary to local deposition and also systemic absorption. For instance, dysphonia is secondary to local deposition, which leads to myopathy of laryngeal muscles, possible candidiasis, and it can also cause mucosal irritation. Spacer devices may help to reduce this risk. Oropharyngeal candidiasis can also be a result of local deposition and spacer devices may also help to reduce this risk. Contact hypersensitivity can occur from local deposition on the skin. This is more commonly seen with budesonide. The next steps would be to confirm with patch testing, then switch to an inhaled corticosteroid that does not cross react with budesonide. These include beclomethasone, mometasone, and fluticasone. In terms of systemic absorption adverse effects, this includes adrenal insufficiency, recommendations in children are to screen asymptomatic children that are at high risk. Though rare, there is an increased risk of pneumonia with systemic absorption of inhaled corticosteroids. This has mostly been seen with fluticasone propionate. However, the

risk of mortality has not been found to be increased. Lastly, an important consideration is growth deceleration from systemic absorption. Further research is needed to determine whether certain inhaled corticosteroids have different effects. In addition, the effect on adult height appears to be small. Systemic corticosteroids have adverse effects that can impact multiple organ systems. For the eyes, it can cause cataracts, glaucoma, and even exophthalmus. Cardiovascularly, this can lead to hypertension, arteriosclerosis, or arrhythmias. Gastrointestinally, you can see gastritis, peptic ulcer disease, or steatohepatitis. For the immune system, you can have increased susceptibility to infections. Hematologically, you can see leukocytosis. Neuropsychiatrically, you can have insomnia, mania, psychosis, dysphoria, depression, or even euphoria. For the musculoskeletal system, you can have osteopenia or osteoporosis, avascular necrosis, and/or myopathy. For the skin, there are multiple adverse effects to include acne, hirsutism, striae, skin thinning, purpura, and ecchymosis. And lastly, for the endocrinologic system, you can have diabetes mellitus or hypoglycemia, adrenal insufficiency, weight gain, cushingoid appearance, or fluid retention. From Chapter 1 we reviewed the mechanisms of inflammation in asthma. I would like to highlight some of the biologic targets of IgE, IL-5, IL-4, and IL-13. Dr. Balkissoon discusses relevant biomarkers in Chapter 2. This is a table of approved asthma biologics in the United States. Starting with omalizumab, which targets IgE, this was approved in the U.S. in 2003 for allergic asthma and later in 2014 for chronic idiopathic urticaria or chronic spontaneous urticaria. It has been approved down to age six. Dosing and frequency is based upon weight, IgE level, and age, but is usually every two or four weeks. This is given subcutaneously in the office for monitoring. Phase 3 clinical trials for omalizumab showed both a reduction in exacerbations and systemic corticosteroid needs. There was no change noted in FEV1. Next, mepolizumab targets IL-5. It was approved in 2015 for asthma and then later in 2017 for EGPA. It has been approved down to age six. Dosing and frequency is every four weeks and depends on the indication. For asthma, it is approved for 100 mg every four weeks, in children 40 mg, and then for EGPA 300 mg. This is given subcutaneously in the office, but has also been approved for home use with prefilled or autoinjectors. In terms of phase 3 clinical trials for mepolizumab, this has been shown to reduce exacerbations, need for systemic corticosteroids, and a minimal increase in FEV1. For reslizumab, this also targets IL-5 and was approved in the U.S. in 2016. This has been approved for ages 12 and up. Dosing for reslizumab is based on weight at 3 mg/kg every four weeks. This is given intravenously in a clinic or infusion center. Phase 3 clinical trials for reslizumab have shown reductions in exacerbations, increased FEV1, but they have not evaluated for systemic corticosteroid reductions. Benralizumab targets IL-5 receptor alpha and was approved in the U.S. in 2017. It's been approved for ages 12 and up. Dosing is 30 mg every four weeks for three doses, then followed by every eight weeks. This is given subcutaneously. In the office there are prefilled versions, but it has also been approved for home prefilled autoinjector use. Phase 3 clinical trials of benralizumab have been shown to reduce exacerbations, reduce need for oral corticosteroids, and also increase FEV1. Lastly, dupilumab, which is an anti-IL-4 receptor alpha and, therefore, impacts the IL-4 and IL-13 pathways. It was approved in the U.S. in 2017 originally for atopic dermatitis. Soon following in 2018, it was approved for moderate to severe asthma and in 2019, also for chronic rhinosinusitis with nasal polyposis. This has been approved for ages 12 years and up. Dosing is typically 600 mg for the first dose followed by 300 mg every two weeks, except for chronic rhinosinusitis with nasal polyposis, which is 300 mg every two weeks. This is given subcutaneously in prefilled syringes and approved for home use. Phase 3 clinical trials of dupilumab have shown reductions in exacerbations, increased FEV1, and reduction and need for oral corticosteroids. Now that I have reviewed the currently approved biologics for severe asthma, Dr. Balkissoon will review the emerging treatments for asthma and related eosinophilic diseases.

Dr. Balkissoon:

Well, Eileen's covered the biologics that look at anti-IgE, anti-IL-5, and anti-IL-4 and IL-13, but there are newer emerging biologics that will help us to deal with patients who still do not respond to the current biologics that are available. There are a host of cytokines, which are called alarmins, which are released from the bronchial epithelium and have played a critical role in being able to stimulate, not only Th2 inflammatory pathways, but also non-Th2 pathways. These include such things as TSLP, IL-25, and IL-33. Of these alarmins, the cytokine that has probably been the most studied, is TSLP. Tezepelumab is a monoclonal antibody that is geared towards TSLP and is able to block it. A pivotal study was a 52-week, phase 2, randomized, double-blind controlled trial that was multicenter and looked at three different doses delivered subcutaneously versus placebo, which was given every four weeks. The doses included a 70 mg dose and a 210 mg dose given subcutaneously every four weeks and a 280 mg dose that was given every two weeks. There were 137 patients in each group who were on LABA and medium-high dosing corticosteroids, and they had to be Th2-high patients witnessed by having an IgE that was greater than a hundred and a blood eosinophil count that was, at least, 140 eosinophils per microliter. Looking at the results, first looking at the reductions and exacerbations, we can see that there was a significant reduction in exacerbations by 62%, 71%, and 66%, respectively, for the 70 mg dose, 210 mg dose, and 280 mg dose. Further, what was interesting was that these signals were found regardless of whether or not the patient had a high exhaled nitric oxide level, but their Th2 status was, or what their underlying blood eosinophil count was. If we look at exhaled nitric oxide levels, we're also able to identify the fact that there was a significant reduction in exhaled nitric oxide compared to placebo and that indeed the highest dose, the 280 mg dose, had the greatest reduction in exhaled nitric oxide levels. Other findings included that the FEV1 was improved in all the groups with 120, 130, and 150 cc improvement, respectively, compared to placebo and, overall, it is, I think, most important that these findings all seem to occur regardless of the underlying T2 signals. Here we see a summary of the studies that have been done with the alarmins to date. As you

can see, tezepelumab is currently being studied, and it's at phase 3 level of studies. For anti-IL-33 agents, these are at the phase 2 level, and for anti-IL-25, no studies are available to date. Other biologics that have been looked at are the anti-IL-13 agents, lebrikizumab and tralokinumab, and the anti-IL-17 agent brodalumab. Unfortunately, all trials that have been done with these have failed to show significant benefit for patients with severe asthma, and further studies for these have been discontinued. This chart summarizes the biologics that continue to be in either phase 2 or phase 3 trials. They include anti-IL-33 agents, anti-IL-25 agents, and anti-TSLP agents, as previously mentioned. In addition to these T2 biologics, there are also these newer, non-T2 biologics targeting non-T2 pathways. Examples include Navarixin, which is a chemokine receptor 2 antagonist and imatinib, which is a kit antagonist as well. These continue to be examined for non-T2 asthma. Other proposed targets include such things as IL-6 or IL-9, but there are no studies at the current time being looked at. As mentioned previously, in addition to biologics being used for asthma, there may be applications for other significant eosinophilic conditions. Certainly with chronic rhinosinusitis and nasal polyposis, there's a robust line of studies that have looked at a number of biologics including dupilumab, which was actually approved in 2019 in addition to mepolizumab, benralizumab, omalizumab, tezepelumab, and anti-IL-33 antagonist, CRTH2 antagonist, and the thromboxane antagonist, ifetroban. For other eosinophilic conditions, there are several trials being done at the phase 2 or phase 3 level including EGPA, hypereosinophilic syndrome, and ABPA. For EGPA, mepolizumab was actually approved in 2017, and there are studies ongoing for benralizumab as well. For hypereosinophilic syndrome, mepolizumab and benralizumab are still involved in phase 2 or phase 3 studies. For ABPA, there've actually been several biologic studied including omalizumab, for which there was a randomized control trial, and mepolizumab, benralizumab, and dupilumab have all produced case studies. None of these drugs have been approved for use for ABPM at the current time, however. So, in conclusion, we recognize that asthma is actually a spectrum of diseases, and there are different pathologic and clinical phenotypes. We understand the underlying immunology of asthma better, and it's helping us to define, not only phenotypes, but significant endotypes as well, which is helping us to be more precise in targeting our asthma patients. In addition to that, we also appreciate that there are several eosinophilic conditions that are concomitantly present in patients who have severe asthma that may be amenable to treatment with biologics as well. So, tailoring our treatment to the various phenotypes and endotypes of asthma, as well as these other concomitant eosinophilic conditions, is the new frontier in precision medicine for patients with asthma.

Dr. Wang:

Well, with that, on behalf of Dr. Balkissoon and myself, we'd like to thank you for joining us today on ReachMD.