Current and Emerging Biologic Therapies for Asthma and COPD

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Historical treatments for asthma and COPD have primarily focused on addressing the underlying inflammation and bronchoconstriction that result in air flow obstruction symptoms, including shortness of breath, cough, chest tightness, and mucus production. However, in the past several years, new research into the underlying pathophysiology of asthma and COPD has led to novel targeted therapies that address the underlying pathways that cause these obstructive disorders. As we have gained a better understanding of underlying disease mechanisms, we have begun to use biomarkers and endotypes to personalize our approach to therapy. Targets for asthma and COPD include immunoglobulin E, interleukin 5, interleukin 4/interleukin 13, thymic stromal lymphopoietin, interleukin 17, tyrosine kinases, and others. The new biologics are generally safe and well tolerated, and are bringing promise and hope of personalized therapy to patients with severe asthma. *Key words: asthma; COPD; biologics; IL-5; IL-4/IL-13; TSLP; nonTh2; imatinib.* [Respir Care 2018;63(6):699–707.

Introduction

Asthma and COPD continue to affect millions of individuals annually, with millions of emergency department visits, hundreds of thousands of hospitalizations, and thousands of deaths annually.[1] Historical treatments primarily focused on addressing the underlying inflammation and bronchoconstriction that result in the air flow obstruction symptoms, including shortness of breath, cough, chest tight-

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ness, and mucus production. However, in the past several years, new research into the underlying pathophysiology of asthma and COPD has led to novel targeted therapies that address the underlying pathways that cause these obstructive disorders (Table 1).

Current Approaches to Asthma and COPD Management

Current asthma guidelines, including those developed by the National Asthma Education Prevention Program[2] and the Global Initiative for Asthma,[3] recommend a stepwise approach to management, with initiation of inhaled corticosteroids in patients with mild persistent asthma, with increased inhaled corticosteroids dosing; the addition of long-acting β agonists; leukotriene modifiers, including montelukast or zileuton; and long-acting anticholinergics, for example, tiotropium, to those who remain poorly controlled. For COPD, guidelines recommend initiation of long-acting β agonists with or without inhaled corticosteroids, or long-acting anticholinergics, and, in severe cases, the addition of phosphodiesterase inhibitors, including roflumilast.[4] For some patients with asthma or COPD that fail to respond to these therapies, likely due to poor adherence or underlying disease heterogeneity, oral corticosteroids are often used. However, these are associated with significant systemic toxicity, including adrenal insufficiency, weight gain, hypertension, cataracts, glaucoma, and osteoporosis. Thus, a major question is what to do for those patients who continue to have symptoms or exacerbations despite triple therapy with inhaled corticosteroids, long-acting β agonists, and long-acting antimuscarinics or other controllers.

Approaching Severe Asthma and COPD

The first step in managing patients with severe asthma and COPD involves confirming the diagnosis, assessing adherence, evaluating environmental factors that could be contributing to disease manifestations (eg, environmental allergens or smoke exposure), and investigating comorbid disease that could be contributing to symptoms (eg, gastroesophageal reflux disease, sinusitis, chronic respiratory tract infections, obstructive sleep apnea, or vocal cord dysfunction).[5] Next, it is important to characterize the type of disease by phenotyping and endotyping the patient.[6] Phenotype refers to the observable characteristics of a specific

Table 1. Biologics Cleared or in Late-Stage Development for Asthma and COPD

Drug	Phase	Dosing	Frequency	Route	Exacerbation Reduction Rate (vs Placebo) (%)	Increased FEV_1 (vs Placebo) (mL)
Reslizumab Anti–IL-5	Cleared in 2016	3.0 mg/kg	Q4W	Intravenous	50–59	110–126
Mepolizumab Anti–IL-5	Cleared for asthma 2015; currently phase 3 COPD	100 mg	Q4W	Sub-Q	53	98
Benralizumab Anti–IL-5 Receptor	Cleared for asthma 2017; currently phase 3 COPD	30 mg	Q8W (first 3 doses every 4 wk)	Sub-Q	36–55 (Q4W frequency); 28–70% (Q8W frequency)	0–125
Omalizumab Anti-IgE	Cleared for asthma 2003; Cleared urticaria	125–375 mg (based on weight/IgE level)	Q2W or Q4W (depending on weight/IgE level)	Sub-Q	33–75	NS
Dupilumab Anti–IL-4 Receptor	Cleared in 2017 for atopic dermatitis; phase 3 for asthma	200–300 mg	Q2W	Sub-Q	59.9–80.7	390–430
Tezepelumab Anti-TSLP	Phase 3 for asthma	70–280 mg	Q2–4 W	Sub-Q	61–71	110–150

IL = interleukin
Ig = immunoglobulin
TSLP = thymic stromal lymphopoietin
Q4W = every 4 weeks
Sub-Q = subxutaneous
Q8W = every 8 weeks
Q2W = every 2 weeks
NS = not significant

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disease entity, such as age, sex, race, environmental or allergic exposures, and time of disease onset. Endotype refers to the mechanism of the underlying disease as it relates to cellular, cytokine, or mediator involvement (eg, eosinophilic COPD, immunoglobulin [Ig] E–mediated asthma, interleukin [IL] 5–mediated asthma). Endotyping depends on the use of biomarkers that reflect an underlying disease mechanism. Currently used biomarkers include eosinophils in the blood or sputum, exhaled nitric oxide, IgE levels, and specific cytokines in the blood or sputum. By phenotyping and endotyping patients with asthma and COPD, one can personalize approaches to treatment for those patients who need add-on therapies.

Personalizing Asthma and COPD Management With Novel Biologic Therapies

Our understanding of the underlying pathophysiology of asthma and COPD has evolved significantly over the past decade. We have come to appreciate how heterogeneous these entities are, how many different cellular elements are involved, how many different cytokines and mediators are implicated, and how dynamic these diseases may be from one point in time to another. One broad way of classifying endotypes is based on activation of specific cytokines. Allergens generally cause activation of T helper cell type 2 (Th2) and innate lymphoid cells that activate IL-4, IL-5, and IL-13 to activate eosinophils and mast cells among others; this is referred to as type 2 inflammation. In contrast, viruses, bacteria, and irritants generally activate non–type 2 cells, including Th17 cells, that activate neutrophils through IL-6 and IL-17, among others. This new understanding has led to the development of precision interventions with biologic therapies that target specific elements of disease pathophysiology. Below are some of the pathways and new targeted therapies that are emerging for patients with asthma and COPD.

Current Targets

IgE

Inhaled allergens stimulate the production of IgE by B lymphocytes. B lymphocytes differentiate into plasma cells (the ε-switch), which produce and release IgE antibodies into circulation. IgE circulates in the blood, eventually binding to high-affinity IgE receptors on mast cells in tissue or peripheral blood basophils. When patients reencounter offending allergens, binding of the allergen with IgE induces the release of inflammatory mediators, such as histamines or leukotrienes, and which leads to the bronchoconstriction associated with asthma exacerbations.

Omalizumab was the first monoclonal antibody cleared for the management of asthma. Omalizumab binds to IgE, which inhibits the binding of IgE to the high-affinity IgE receptor on mast cells and basophils. This leads to reduced binding of IgE on these cells, which limits the degree of release of mediators of the allergic response. Omalizumab was cleared for use in patients age >12 y in 2003[7,8] with allergic asthma (and subsequently down to age 6 y), after it was demonstrated to significantly reduce asthma exacerbations in patients with allergic asthma that was poorly controlled, despite the use of inhaled corticosteroids, and, subsequently, was demonstrated to reduce exacerbations in patients with more severe disease in patients on inhaled corticosteroids and long-acting β agonists. Omalizumab is dosed based on IgE levels and body weight, and is administered every 2–4 weeks. More recent studies have shown that omalizumab has its greatest efficacy in patients with type 2 inflammation as characterized by elevated levels of blood eosinophils, periostin, or exhaled nitric oxide.[9] Although it is generally well tolerated, omalizumab injections can cause local pain at the injection site, and, rarely, hypersensitivity reactions. Omalizumab is not indicated for COPD.

IL-5

IL-5 is a cytokine that regulates proliferation, maturation, migration, and effector functions of eosinophils. It is produced by several cells, including Th2 lymphocytes, innate lymphoid cells, natural killer cells, eosinophils, basophils, and CD34+ cells. IL-5 messenger ribonucleic acid is increased in patients with asthma, is correlated with asthma severity, and is inducible by allergen exposure. Eosinophils have been implicated in both asthma and COPD, and contribute to airway inflammation through IL-5–mediated release of a variety of different granular proteins, including major basic protein, eosinophilic cationic protein, and eosinophil-derived neurotoxin. Because approximately half of patients with asthma and one third of the patients with COPD demonstrate airway eosinophilia that is associated with disease severity, IL-5 has become a major target for both asthma and COPD,[10] and, currently, 3 biologics that target IL-5 or its receptor have been cleared by the FDA.

Although early trials of mepolizumab, a monoclonal antibody that targets the IL-5 ligand, were successful in decreasing eosinophil counts, mepolizumab initially was not demonstrated to improve lung function across broad asthma populations.[11,12] However, in trials that evaluated patients with sputum or blood eosinophilia, despite high-dose inhaled corticosteroid or prednisone use, mepolizumab caused a significant decrease in exacerbations when compared with placebo.[13-15] Mepolizumab was cleared in 2015 in patients with eosinophilic asthma ages ≥12 y.

Reslizumab, another monoclonal antibody that targets IL-5, is administered intravenously (3 mg/kg) on a monthly

basis and has been shown to have significant effects not only on asthma symptoms but also on lung function and exacerbations when compared with placebo.[16] Reslizumab was cleared in 2016 for patients ≥18 y with eosinophilic asthma.

Benralizumab, a monoclonal antibody that targets IL-5Rα, was cleared for use in eosinophilic asthma in 2017. In early studies, benralizumab was shown to decrease blood, sputum, and airway eosinophils, and, more recently, was also demonstrated to reduce asthma exacerbations, improve lung function, and reduce systemic corticosteroid dosing by as much as 75%.[17-20] One advantage that benralizumab has is that it may be administered subcutaneously every 8 wk after the first 3 monthly doses. In addition to blocking the IL-5 receptor and preventing the IL-5 ligand from binding and activating the eosinophil, it also may get bound to natural killer cells, which may attack the eosinophils and result in eosinophilic depletion.

Anti–IL-5 and COPD

As of early 2018, no anti–IL-5 therapies have been cleared for use in COPD. However, 2 mepolizumab phase 3 studies showed improvements in exacerbation frequency in subjects treated with mepolizumab who had an eosinophilic phenotype and a history of COPD exacerbations, despite triple therapy.[21] In the METREX study,[21] among subjects with an eosinophilic phenotype (ie, ≥150 cells/μL at screening or ≥300 cells/μL anytime during the previous year), those treated with mepolizumab 100 mg once monthly had a significantly lower annual moderate-to-severe exacerbation rate compared with subjects treated with placebo (1.40 vs 1.71, $P = .04$). In the METREO study, the annual exacerbation rate was not significantly different for the mepolizumab 100 mg, mepolizumab 300 mg, and placebo treatment groups (1.19, 1.27, and 1.49, respectively). These results indicate that there is likely some role for eosinophils in COPD but that more study is needed.

Although reslizumab has yet to be formally evaluated in clinical trials for COPD, in a phase 2 trial in subjects with COPD with sputum eosinophilia (≥3%), benralizumab treatment did not significantly reduce the annual rate of moderate or severe exacerbations.[22] However, significant improvements in FEV_1 were observed in the overall population, and the results of prespecified subgroup analyses by baseline blood eosinophil count with benralizumab versus placebo have led to ongoing phase 3 trials to evaluate benralizumab in COPD.

Future Targets

IL-4/IL-13

IL-4 and IL-13 are cytokines that are found in increased levels in the airways and sputum of subjects with asthma. IL-4 is produced primarily by Th2 cells and mast cells, whereas IL-13 is produced by Th2 cells, mast cells, eosinophils, and basophils. IL-4 and IL-13 share a common receptor, IL-4Rα, and act through the STAT 6 signaling pathway. IL-4 promotes Th2 cell development and B-cell isotype switching, and affects chemokine production by airway epithelium. IL-13 has effects on hematopoietic cells, airway epithelium, smooth muscle, fibroblasts, and the endothelium, which promote the allergic phenotype.

Dupilumab, a monoclonal antibody that inhibits the IL-4Rα subunit, was cleared in 2017 for treatment of atopic dermatitis and is being evaluated by the FDA for use in asthma. Dupilumab was superior to placebo in preventing asthma exacerbations and in improving lung function in patients receiving long-acting β agonist and inhaled steroids, with or without blood or sputum eosinophilia.[23,24]

Lebrikizumab and tralokinumab, monoclonal antibodies that target IL-13, initially yielded benefits with respect to airway function when compared with placebo in patients with uncontrolled asthma, despite inhaled steroid use in some patients with high periostin or dipeptidyl peptidase-4 levels. However, neither of these therapies was shown to be beneficial in phase 3 studies in targeted populations and are no longer being pursued in asthma.[25,26] Dupilumab, lebrikizumab, and tralokinumab have not been extensively studied in COPD.

Thymic Stromal Lymphopoietin and IL-33

Thymic stromal lymphopoietin, a relatively novel target for asthma and COPD, is an epithelial-cell–derived cytokine that drives allergic inflammatory responses by activating dendritic cells and mast cells. Tezepelumab (AMG 157), a humanized monoclonal antibody that binds thymic stromal lymphopoietin, was evaluated in a phase 2 randomized double-blind placebo-controlled trial over a 52-week treatment period.[27] Three different doses of tezepelumab resulted in annualized asthma exacerbation rates at week 52 that were lower by 61, 71, and 66% compared with the placebo group ($P < .001$ for all comparisons).[27] Prebronchodilator FEV_1 at week 52 was also higher in all tezepelumab groups compared with placebo.[27] Overall, subjects treated with tezepelumab had lower rates of asthma exacerbations compared with those who received placebo, independent of baseline blood eosinophil counts, exhaled nitric oxide levels, or Th2 status.[27] Anti–IL-33 therapies are currently in development, but, similar to anti–thymic stromal lymphopoietin, target many of the inflammatory pathways that are involved in activation of many of the cytokines noted above.

Non-Th2 Inflammation Targets

All of the cleared biologics and most of the biologics currently in development focus on Th2 inflammatory pathways.

This has left a large unmet need for patients with severe asthma without significant Th2 inflammation. IL-6 and IL-17 may promote both Th2 and non–type 2 inflammatory cascades; this makes these 2 cytokines targets of interest in mixed inflammatory obstructive airways diseases.

IL-17

IL-17, a cytokine produced by Th17 cells, plays an important role in the immunologic responses seen in asthma. Increased quantities of IL-17 have been isolated in blood, sputum, and human airway cells of patients with asthma. IL-17 receptor activation leads to the secretion of several inflammatory mediators, including IL-1β, IL-6, tumor necrosis factor alpha, and granulocyte-macrophage colony-stimulating factor, which ultimately leads to neutrophil recruitment. Brodalumab is a human monoclonal antibody that binds IL-17RA, which inhibits signaling of IL-17 and IL-25. In a phase 2a trial of adults with moderate-to-severe asthma, a prespecified subgroup that demonstrates high bronchodilator reversibility reported improved asthma control questionnaire scores,[28] but no other clinically meaningful differences were found between the brodalumab groups and placebo, and this therapy has not been pursued further in asthma or COPD.

CXCR2 and CCR3

CXCR2 is a potent chemo-attractant for neutrophils that is being investigated in asthma and COPD. CXCR2 antagonists decrease IL-8 levels and have shown promise in early human trials.[29] Navarixin, a CXCR2 receptor antagonist, reduced sputum and blood neutrophils and trend toward better asthma control based on Asthma Control Questionnaire (ACQ) but no significant change in FEV_1.[30] An antisense oligonucleotide CCR3 antagonist (co-administered with an antisense oligonucleotide that targets the βc subunit of the IL-3, IL-5, and granulocyte-macrophage colony-stimulating factor receptors) has shown some efficacy in phase 2 trials, decreasing sputum eosinophils in response to allergen challenge.

Tyrosine Kinases

Stem cell factor and its receptor, KIT, are central to mast cell homeostasis. Imatinib is a KIT inhibitor that was recently evaluated in a randomized double-blind placebo-controlled multicenter 24-week trial in subjects with severe asthma with airway hyper-responsiveness and poor asthma control despite maximum medical therapy.[31] Imatinib inhibited mast cells and reduced airway hyper-responsiveness compared with placebo.[31] These results indicated that KIT-dependent processes contribute to pathobiologic processes in severe asthma and may be appropriate targets for treatment of this disease.[31] Further studies of imatinib in asthma are currently being planned, and other tyrosine kinase inhibitors that may affect both airway inflammation and remodeling are being tested in animal models and in early clinical trials.

Summary and Future Directions

We are in an exciting era in the management of asthma and COPD. We recognize that asthma and COPD are heterogeneous entities, but we are gaining a better understanding of underlying disease mechanisms and are using biomarkers and endotypes to personalize our approach to therapy. The new biologics are generally safe and well tolerated, but expensive, and it remains unclear to physicians and payers how to choose between therapies that may benefit patients with similar response profiles. It also remains unclear whether some patients may benefit from combinations of biologics that may affect different pathways that are simultaneously active in a given patient. Although the era of biologics has emerged in asthma, the focus has been on type 2 inflammation, whereas the absence of non–type 2 targeted therapies remains an unmet need. Novel targeted biologic therapies are not cleared in COPD, but the horizon is bright, with many studies ongoing. Although long-term safety studies and real-world efficacy studies are certainly warranted, the new biologics offer an opportunity to provide precision therapies that will improve outcomes in patients with asthma and COPD for years to come.

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Discussion

Strange: I would make a cautionary note on your search for specific genotypes or endotypes. In our alpha-1 antitrypsin experience, in which we know the gene, sometimes the genotype gives you a patient with asthma, bronchiectasis, emphysema, and sometimes it isn't all in the genes. So, sticking with phenotyping might be the way to go.

Wechsler: There's been a huge effort to try to identify specific genetic predictors of responsiveness to different asthma therapies. With the β agonists, we talked about the arg/arg genotype, and there are also pharmacogenetics looking at inhaled steroids. It might be that we need to identify specific responders to therapies because of their cost, by doing pharmacogenetics. But I still feel like pharmacogenetics is somewhat in its infancy despite the fact that there have been thousands of papers published, 95% of which are review articles as opposed to substantive articles that have changed practice.

Peters: So you brought up the point that, when you look at mepolizumab studies, the reduction of exacerbations is probably a key feature of these therapies. When you actually look at just emergency department visits and hospitalizations rather than lumping oral corticosteroids in, how effective are-

they? In looking at the original 2 studies in mepolizumab,[1,2] when they evaluated a broad section of subjects with asthma rather than subjects with severe asthma with frequent exacerbations, they really could not show significant changes in quality of life or symptom control. How much data are there for the monoclonal antibodies other than omalizumab that document quality of life and reduction in symptoms? When Busse et al[3] tried to stop omalizumab in their study, they reported that their subjects relapsed. That has not been our experience in San Antonio; we have been able to taper some patients off omalizumab and followed up on them to document stability. Do you feel that once you start patients on these monoclonal therapies that you are expecting to keep them on lifelong?

Wechsler: I'll address the second question first, which is the issue of how long should we treat these patients. These drugs have only been available, the anti-IgE has been around for a while, and people either respond or do not respond to these therapies. There have been some studies that show that, if you stop the omalizumab, then there is actually an increase in exacerbations in those who had been responding if they stop it. The same thing has been demonstrated with the anti–IL-5 therapies. If you stop it, within 3 or 4 months, then there is an increase in exacerbations. There have been some open-label extension studies that have demonstrated that, in people who were responding to therapy and then came off therapy slowly, they had an increase in their eosinophils over a few months and they had increased risks of exacerbations over that time. The first question was?

Peters: When you omit the studies that include exacerbations defined by the need for oral corticosteroids and look at reductions in severe exacerbations (requiring emergency department visits or hospitalizations), do these therapies still show efficacy?

Wechsler: Right, so if you want to look at just emergency department visits and hospitalizations are much less common than asthma exacerbations. And asthma exacerbations are defined as $\geq$3 d of systemic corticosteroids for increased symptoms of asthma. Some people look at asthma deterioration. That's another definition of asthma exacerbations as sort of a composite end point of deterioration. We've looked at that as well.[4] Emergency department visits and hospitalizations are much less common; they're $<$5-10% of all exacerbations. However, with each of these biologics, if you do a subgroup analysis, there's a reduction in those patients by approximately 70% with reslizumab and mepolizumab. With regard to benralizumab, there's a benefit there as well.[5] Again, those events are much less common, but there is a significant impact on those outcomes. Frankly that's what payers are most interested in. They're interested in those outcomes in specific, and there's a 50-70% reduction with different monoclonals as well as with bronchial thermoplasty, by the way.[6]

Lugogo: I think the vast majority of prescribers of omalizumab are actually allergists. Furthermore, most of the drug is prescribed by a small percentage of the total population. So, for instance, at our institution, there might be 1 or 2 clinicians who use biologics and then there are 40 other clinicians who almost never give any patient biologics. Apart from encouraging phenotyping and things like that, I wonder how we can encourage our fellow pulmonologists to prescribe these medications to patients with severe asthma. This is similar to my comments about low utilization of alpha-1 replacement therapy. Of course, in contrast, biologic drugs in asthma have been shown to have profound effects. In spite of this, I think there is a lot of resistance to giving very expensive therapies to patients particularly because oral corticosteroids are cheap. There is also this idea that patients with asthma who are not well controlled are somewhat to blame because they are not adherent and don't take their inhaled medications. This has resulted in a mental block when it comes to taking up new therapies. Therefore, how should we as providers who are leading the charge in terms of the care of patients with asthma address this so there is some uptake? Because there are some patients who would really benefit from these therapies who are not receiving them at this time.

Wechsler: Looking at some of the prescription data, only approximately 10-15% of pulmonologists prescribe biologics for asthma. Obviously none for COPD because it isn't cleared for COPD as of yet. Now a part of it is the heterogeneity of pulmonologists, some just do critical care, some just do pulmonary fibrosis, and some just do lung cancer. You wouldn't expect those people to prescribe mepolizumab or reslizumab for asthma. But most physicians out there in a clinical practice, they do see asthma. Part of the problem is logistics. When omalizumab came out, most pulmonologists were not set up to give shots. They weren't set up in their regular clinic to store the drug, prepare the drug, and things like that. So there tended to be a huge referral to allergists who are use to giving allergy shots on a regular basis. That being said, with these new therapies coming out, I think we have to educate physicians, pulmonologists, allergists, even primary care physicians that there are other options and that these are quite effective in a subset of patients, and that patients who are on systemic corticosteroids, in particular, I view it unacceptable for people to be systematic corticosteroids in this day and age. I think it's our job, and part of what we're doing here is to educate respiratory therapists about what is out there

but also primary care physicians so they say, "Okay, there are these newer therapies that are expensive but they have a significant impact in terms of pharmacoeconomics but, most importantly, reduction in adverse effects of systemic corticosteroids, and also improvement in quality of life and efficacy". Many of the studies that have been done have demonstrated those benefits as well, and I think that's the most important thing. Most of our patients who are on these therapies and continue on them do really well and like being on them. It can be somewhat of a nuisance. Hopefully, over time, it will result in drugs that are given every 8 weeks or maybe home injectables so they won't need to come into the office. I think we need to educate about efficacy of these therapies. It's also important to advocate for reduction in cost with the pharmaceutical industry. Although the sticker price is $32,000/year, most insurers or payers don't pay that, they broker some kind of a deal. So that may make more pharmacoeconomic sense.

MacIntyre: From a practical perspective, say you have a really tough patient with asthma who's been difficult to control on routine medications. What's the Wechsler protocol for assessing biomarkers and making decisions?

Wechsler: The first thing I do is an extensive workup; make sure they have asthma. Part of that extensive workup that isn't done most places is that we do bronchoscopies on those patients with severe conditions to try to identify whether they have some kind of infection going on, whether they have vocal cord dysfunction, whether they have significant gastroesophageal or laryngopharyngeal reflux, and we try to treat those things. But while we're doing that workup we also include blood eosinophils and nitric oxide, and check their IgE level. In some patients, if their phenotype is suggestive, we will also do cystic fibrosis and alpha-1 antitrypsin testing, and we have identified several patients who had unexpected alpha-1 antitrypsin deficiency by doing that kind of testing in our cohort. That would be the first step. Some places do a lot more sputum, like McMaster University in Hamilton, Ontario and University of California, San Francisco. Then, I will try to identify what the predominant biomarker that's going. Do they have high eosinophils versus low eosinophils? I'll also use a little of their phenotypic characteristics because reslizumab is an intravenous preparation that's dosed in mg/kg, and, in the patients who is more obese, I might give reslizumab instead of mepolizumab. We'll see when benralizumab comes out but, hopefully, that will be an effective therapy that can be given every 8 weeks, which some patients might prefer as well, and, if a patient has low eosinophils and low nitric oxide, then I am less likely to use one of these therapies. There is a paucity of therapies, but it's possible that, in those patients, right now I might do bronchial thermoplasty, if they have no inflammation, no eosinophils, low IgE, and low nitric oxide. Maybe when dupilumab comes out, it will be an effective therapy for those patients, in addition to the patients with type-2 inflammation with eosinophilia.

George: I think it's really interesting when the payers are saying that, in some respects, they want to withhold these costly therapies from patients because they have been non-adherent to other treatments. But there is nothing that will quickly sort out which patients are truly motivated enough and warrant some kind of biologic therapy. I think about patients I've treated with anti-IgE coming in twice a month, and, each time they come, they get 3 injections based on this chart, and someone does that every other week for years on end, I think it's a really quick point to make about trying to separate out the patients who really are non-adherent versus those who are motivated to do something to get better.

Wechsler: What's been shown is that those who respond to these therapies tend to stay adherent. And if they stop being adherent, they feel miserable and go back. Another point is that there was one study, published by Busse et al,[7] that shows that, for some therapies, such as anti-IgE, it might be beneficial to give it seasonally during allergy season or at the beginning of school and that might be just as good in that cohort. It was an inner-city asthma study that demonstrated that. I agree with you, and we'll see with some of the therapies, like benralizumab, when that comes out at every 8 weeks, how adherent do you really need to be? With the dupilumab study I showed you, the subjects could actually stop their inhaled steroids long-acting β agonists and still had an 87% reduction in their exacerbations.[8] So, this could have a significant impact, particularly in those patients who are non-adherent. You're getting these therapies and they're not every day but every 2, 4, or 8 weeks might be beneficial, particularly if there is home administration.

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