

Changing Paradigms in the Treatment of Severe Asthma: The Role of Biologic Therapies



Rohit K. Katial, MD^a, Greg W. Bensch, MD^b, William W. Busse, MD^c, Bradley E. Chipps, MD^d, Joshua L. Denson, MD^{e,f}, Anthony N. Gerber, MD, PhD^{e,g}, Joshua S. Jacobs, MD^h, Monica Kraft, MDⁱ, Richard J. Martin, MD^j, Parameswaran Nair, MD, PhD, FRCP, FRCPC^k, and Michael E. Wechsler, MD^e *Denver, Aurora, Colo; Stockton, Sacramento, Walnut Creek, Calif; Madison, Wis; Tucson, Ariz; and Hamilton, Ontario, Canada*

Cytokine antagonists are monoclonal antibodies that offer new treatment options for refractory asthma but will also increase complexity because they are effective only for patients with certain asthma subtypes that remain to be more clearly defined. The clinical and inflammatory heterogeneity within refractory asthma makes it difficult to manage the disease and to determine which, if any, biologic therapy is suitable for a specific patient. The purpose of this article is to provide a data-driven discussion to clarify the use of biologic therapies in patients with refractory asthma. We first discuss the epidemiology and pathophysiology of refractory asthma. We then interpret current evidence for biomarkers of eosinophilic or type 2-high asthma so that clinicians can determine potential treatments for patients based on knowledge of their effectiveness in specific asthma phenotypes. We then assess clinical data on the efficacy, safety, and mechanisms of action of approved and pipeline biologic therapies. We conclude by discussing the potential of phenotyping or endotyping refractory asthma and how biologic therapies can play a role in treating

patients with refractory asthma. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;5:S1-S14)

Key words: Severe asthma; Refractory asthma; Biologic therapy; Monoclonal antibody; Eosinophil; FeNO; Periostin

Although a substantial proportion of suboptimal outcomes in asthma is related to poor adherence as well as both avoidable and unavoidable environmental exposures, increasing evidence suggests that there remain a group of patients with refractory asthma in whom standard therapies are ineffective.¹ Cytokine antagonists are monoclonal antibodies that offer new treatment options for refractory asthma but are effective only for patients with certain asthma subtypes. These specific asthma subtypes and the best measures to identify responders are still becoming recognized. Clinicians need to be able to distinguish between difficult-to-treat asthma, in which the patient is capable of asthma control with currently available treatments, and refractory asthma, in

^aDepartment of Medicine, Division of Allergy and Clinical Immunology, National Jewish Health, Denver, Colo

^bAllergy, Immunology and Asthma Medical Group, Stockton, Calif

^cDepartment of Medicine, Division of Allergy, Pulmonary and Critical Care, University of Wisconsin School of Medicine and Public Health, Madison, Wis

^dCapital Allergy and Respiratory Disease Center, Sacramento, Calif

^eDepartment of Medicine, Division of Pulmonary, Critical Care and Sleep Medicine, National Jewish Health, Denver, Colo

^fDivision of Pulmonary Sciences and Critical Care Medicine, School of Medicine, University of Colorado at Denver, Anschutz Medical Campus, Aurora, Colo

^gDepartment of Biomedical Research, National Jewish Health, Denver, Colo

^hAllergy and Asthma Clinical Research, Inc., Walnut Creek, Calif

ⁱDepartment of Medicine, Asthma and Airway Disease Research Center, University of Arizona Health Sciences, Tucson, Ariz

^jDepartment of Medicine, National Jewish Health, Denver, Colo

^kDepartment of Medicine, McMaster University, Hamilton, Ontario, Canada

The authors were part of an expert panel hosted by the Cohen Family Asthma Institute at National Jewish Health in Denver, Colorado. This activity is supported by an independent educational grant from Teva Pharmaceuticals.

Conflicts of interest: R. K. Katial has received consultancy fees and travel support from Teva Pharmaceuticals; has received consultancy fees from AstraZeneca and Meda; and has received lecture fees from Meda. G. W. Bensch has received consultancy and lecture fees and travel support from Teva Pharmaceuticals; and payment for lectures including service on speakers bureaus from AstraZeneca. W. W. Busse has received consultancy fees and travel support from Teva Pharmaceuticals; is on the Boston Scientific and Circassia Data Safety Monitoring Boards; is on the ICON Clinical Research Limited Study Oversight Committee; has received consultancy fees from Novartis, GlaxoSmithKline, Genentech, Roche, Pfizer, Merck, Boehringer Ingelheim, Sanofi, AstraZeneca, Takeda, Aerocrine, 3M, and PrEPBiopharm; has received research support from National Institutes of Health (NIH)-National Institute of Allergy and Infectious Diseases (NIAID) and NIH-National Heart, Lung, and Blood Institute; and receives royalties from Elsevier. B. E. Chipps has received consultancy fees and travel support from Teva Pharmaceuticals; has received

consultancy and lecture fees from AstraZeneca, Boehringer Ingelheim, Genentech, Meda, Merck, and Novartis. J. L. Denson declares no relevant conflicts of interest. A. N. Gerber has received consultancy fees from Teva Pharmaceuticals and Revon Systems, the latter outside the current work. J. S. Jacobs has received travel support from Teva Pharmaceuticals; has received consultancy fees from Teva Pharmaceuticals and Sanofi-Aventis; has received lecture fees from Teva Pharmaceuticals; and has received research support from Teva Pharmaceuticals, Genentech, and AstraZeneca. M. Kraft has received consultancy fees from Teva Pharmaceuticals and AstraZeneca; has received research support from the NIH, Chiesi, Roche, and Sanofi; and receives royalties from Elsevier. R. J. Martin has received consultancy fees from Teva Pharmaceuticals and PMD Healthcare; has received research support from MedImmune, NHLBI, and Chiesi Farmaceutici SpA; has received travel support from the Respiratory Effectiveness Group; and is on the advisory boards for AstraZeneca and Genentech. P. Nair has received travel support from Teva Pharmaceuticals; is on the scientific advisory boards for Teva Pharmaceuticals, AstraZeneca, and Sanofi; has received consultancy fees from Teva Pharmaceuticals, Sanofi, Roche, Daiichi Sankyo, Novartis, and Knopp; has received research support from AstraZeneca, Novartis, Sanofi, Boehringer Ingelheim, Roche, Teva Pharmaceuticals, and GlaxoSmithKline; and has received lecture fees from AstraZeneca, Novartis, and Teva Pharmaceuticals. M. E. Wechsler has received consultancy fees from Sepracor/Sunovion, Asthmatx/Boston Scientific, Merck, Regeneron, MedImmune, Ambitbio, Vectura, Sanofi, Teva Pharmaceuticals, Mylan, AstraZeneca, Genentech, Meda, Theravance, Novartis, Boehringer Ingelheim, GlaxoSmithKline, Tunitas, and Gliacure; and is on the advisory board for Teva Pharmaceuticals.

Received for publication November 3, 2016; revised November 21, 2016; accepted for publication November 23, 2016.

Available online January 29, 2017.

Corresponding author: Rohit K. Katial, MD, National Jewish Health, 1400 Jackson Street, Denver, CO 80206. E-mail: KatialR@njhealth.org. 2213-2198

© 2017 American Academy of Allergy, Asthma & Immunology
<http://dx.doi.org/10.1016/j.jaip.2016.11.029>

Abbreviations used

<i>AE</i> - Adverse event
<i>ATS</i> - American Thoracic Society
<i>CI</i> - Confidence interval
<i>CPK</i> - Creatinine phosphokinase
<i>DPP-4</i> - Dipeptidyl peptidase-4
<i>ED</i> - Emergency department
<i>EPR-3</i> - Expert Panel Report 3
<i>ERS</i> - European Respiratory Society
<i>FeNO</i> - Fractional exhaled nitric oxide
<i>FEV₁</i> - Forced expiratory volume in 1 second
<i>GINA</i> - Global Initiative for Asthma
<i>IgE</i> - Immunoglobulin E
<i>ICS</i> - Inhaled corticosteroids
<i>ILC2</i> - Group 2 innate lymphoid
<i>IL-4Rα</i> - IL-4 receptor alpha
<i>LABA</i> - Long-acting β -agonist
<i>NAEPP</i> - National Asthma Education and Prevention Program (US)
<i>OCS</i> - Oral corticosteroids
<i>RR</i> - Relative risk
<i>SAE</i> - Serious adverse event
<i>SC</i> - Subcutaneous
<i>TENOR</i> - The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens
<i>Th2</i> - T helper cell type 2
<i>U-BIOPRED</i> - Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes

which the patient has poor asthma control despite taking high doses of inhaled corticosteroids (ICSs) with or without additional controller medications (including oral corticosteroids [OCSs]) or can maintain control only when taking OCSs. This article aims to clarify the use of biologic therapies by providing clinically relevant, evidence-based information to guide clinicians as new biologic therapies emerge for the treatment of refractory asthma. To facilitate these aims, a panel discussion was held in Denver, Colorado, and hosted by the Cohen Family Asthma Institute at National Jewish Health, bringing together 11 key opinion leaders from the United States and Canada to evaluate the role of emerging biologics and to discuss and debate the distinguishing characteristics of severe asthma, asthma phenotypes in treatment selection, the role of T helper cell type 2 (Th2) pathways in severe asthma, and the efficacy, safety, and mechanisms of action of emerging biologic therapies. In this article, our objectives are to (1) discuss the epidemiology and distinguishing characteristics of refractory asthma, (2) interpret current data on the role of eosinophils in the pathophysiology of refractory asthma, (3) distinguish the treatment approaches that are effective in type 2-high (Th2-high) asthma endotypes, and (4) assess recent clinical data on the efficacy, safety, and mechanisms of action of biologic drugs in asthma. Although we recognize that non-type 2-high asthma remains a considerable challenge, our focus is on patients with type 2-mediated inflammation because to date that is the population that biologic therapies are targeting.

IDENTIFYING THE PATIENT WITH REFRACTORY ASTHMA

Guidelines and publications have referred to poorly controlled asthma by a variety of terms: severe asthma, refractory asthma, severe refractory asthma, difficult/therapy-resistant asthma,

difficult-to-treat asthma, and uncontrolled asthma.¹⁻¹¹ Definitions of these terms often overlap, but the terms do not necessarily refer to the same patient population or the same underlying reasons for poor asthma control.

We define refractory asthma per the definition of Bel et al¹² and the 2014 international European Respiratory Society (ERS)/American Thoracic Society (ATS) guidelines,¹ in which patients with refractory asthma are those for whom alternative diagnoses have been excluded, comorbidities have been treated, triggers have been removed, and compliance with treatment has been checked, but remain poorly controlled or with frequent, severe exacerbations despite the prescription of high-intensity treatment *or* who require systemic corticosteroids to maintain asthma control. This type of high-intensity treatment is referred to as Step 5 or Step 6 in the National Asthma Education and Prevention Program (NAEPP) Expert Panel Report 3 (EPR-3) Guidelines for the Diagnosis and Management of Asthma³ and Step 5 in the Global Initiative for Asthma (GINA) Global Strategy for Asthma Prevention and Management.² However, for those in whom control is poor due to adherence issues and comorbidities, the term applied is “difficult-to-control” asthma. A recent study from the Netherlands reported that 17.4% of the asthma patient population had difficult-to-control asthma despite high-intensity treatment, but once poor medication adherence and incorrect inhaler technique were factored, 3.6% of the asthma patient population had severe refractory asthma.¹³

COSTS OF REFRACTORY ASTHMA

The 2000 ATS Workshop on Refractory Asthma estimated that less than 5% of patients with asthma have high medication requirements to maintain good asthma control or have persistent symptoms, exacerbations, or airflow obstruction despite high medication use.⁵ This subset of patients has disproportionately high health care utilization.⁵ Such patients account for much of the morbidity, mortality, medical resource use, and costs related to asthma care.¹⁴⁻¹⁷ Moreover, both adults and children with uncontrolled asthma have significant health care use as measured by rates of hospitalization in the previous year and the lifetime history of intubation.¹⁸ The cost, both direct and indirect, is particularly high in children with very poorly controlled asthma versus children with not-well-controlled or well-controlled asthma.¹⁹ In the Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) observational study of children aged 6-12 years, mean annual total asthma costs in children with very poorly controlled asthma were more than twice as those in children with not-well-controlled asthma or well-controlled asthma.¹⁹

HETEROGENEITY OF ASTHMA

Clinically, there are differences among patients in terms of symptoms, airway function (eg, forced expiratory volume in 1 second [FEV₁]), airway architecture, airway hyperresponsiveness, degree and type of inflammation, susceptibility to exacerbations, and response to corticosteroids. In addition, clinicians encounter many types of populations, including patients who respond well to standard treatment with ICSs and/or long-acting β -agonists (LABAs), patients with comorbidities, and patients who are exacerbation-prone but between exacerbations require very little medication.

Physiologic abnormalities in asthma appear to be defined early in life. The Melbourne Asthma Study, a long-term cohort study that began in 1964, found that airflow limitation (FEV₁) persisted throughout life, regardless of new therapies that became available over 50 years.²⁰ In addition, data from Rochester, Minnesota, showed that asthma began before age 4 in 80% of asthma cases.²¹ Recent cluster analyses within refractory asthma have highlighted heterogeneity of asthma in clinical presentation.²²⁻²⁴ In a recent study of the British Thoracic Society Severe Refractory Asthma Registry, cluster analysis identified 5 clusters within refractory asthma: (1) atopic, early onset asthma with high exacerbation frequency and poor lung function but the greatest bronchodilator reversibility, (2) late onset disease in obese patients with frequent exacerbations and near-normal lung function, (3) nonatopic disease with normal lung function and infrequent exacerbations, (4) late onset with markedly elevated peripheral blood eosinophilia and frequent exacerbations, and (5) asthma with the lowest lung function but the least frequent exacerbations.²⁴ However, the endotypes, or underlying molecular bases for each of these phenotypic clusters, remain to be fully elucidated. Given that individuals with severe asthma can be phenotypically similar yet have heterogeneous responses to systemic corticosteroids, understanding underlying endotypes could help clinicians identify individuals who would most likely benefit from systemic corticosteroid step-up therapy in spite of their potential side effects.²⁵

PREDICTORS OF EXACERBATION RISK IN REFRACTORY ASTHMA

Several studies have investigated clinical features that predict exacerbation risk or asthma symptoms. In the TENOR study, the largest cohort of patients with severe or difficult-to-treat asthma,²⁶ investigators found that the odds of a future asthma exacerbation increased more than 6-fold with a recent exacerbation.²⁷ This result suggests that recent exacerbation history should be part of clinical assessments of patients with severe or difficult-to-treat asthma.²⁷ A subsequent analysis of TENOR data showed that very poorly controlled asthma also predicted future exacerbations.²⁸ Children with consistently very poorly controlled asthma over a 2-year period had a 6.4-fold higher risk of hospitalization, emergency department (ED) visit, or OCS burst compared with children who improved from very poorly controlled asthma to not-well-controlled asthma or well-controlled asthma.²⁸ Adolescents and adults with consistently poorly controlled asthma over a 2-year period were also at higher risk of hospitalization, ED visit, or OCS burst compared with those patients who improved over the 2-year period.²⁸ In a study of adolescents and adults with severe asthma, the greatest predictor of an exacerbation within 6 months was disease severity (GINA step 4 vs GINA step 3), with as-needed reliever use, postbronchodilator FEV₁ (10% predicted normal value), asthma control as measured by the 5-item Asthma Control Questionnaire, and body mass index being smaller but significant predictors of exacerbations.²⁹ Furthermore, comorbidities play a role in difficult-to-control asthma. A recent study by the Severe Asthma Research Program found that blood eosinophils, bronchodilator responsiveness, body mass index, chronic sinusitis, and gastroesophageal reflux disease were associated with exacerbation-prone asthma.³⁰

A multicenter consortium in the European Union has initiated the Unbiased Biomarkers for the Prediction of Respiratory

Disease Outcomes (U-BIOPRED) project to identify phenotypes of severe asthma and new treatment targets in using a systems biology approach.^{31,32} Preliminary reports of baseline characteristics reveal that adult patients with severe asthma are characterized by poor symptom control, a higher exacerbation risk, increased comorbidity, and increased airway inflammation despite high levels of treatment.³¹ Pediatric patients with severe asthma or severe wheeze typically were atopic and, despite high-dose treatment, had more severe exacerbations and impaired quality of life associated with poor asthma control and airway obstruction.³² Thus, children with severe asthma or severe wheeze have a different phenotype than adults with severe asthma.³² Therefore, for patients with refractory asthma, it is important for clinicians to focus on the constellation of data including symptoms, lung function, exacerbation risk, and patient demographics rather than a single marker of disease. Moreover, a recent analysis of U-BIOPRED bronchial biopsies and bronchial epithelial brushings found that severe asthma exists despite suppressed endobronchial tissue inflammation with the proximal airways, suggesting that severe asthma is affected by additional mechanisms in the central airways or altered peripheral airway changes.³³

ELEMENTS OF THE IMMUNE RESPONSE IN REFRACTORY ASTHMA

Although refractory asthma is closely linked with absolute or relative resistance to steroid-based therapies, this simple correlation fails to capture the range of factors that contribute to steroid-refractory disease, including the epithelium, airway smooth muscle, immune cells, immunoglobulin E (IgE) and cytokines, environmental exposures such as viral infections and cigarette smoking, medications, and patient features such as genetics and comorbid disease. Furthermore, the complexity of the immune response in refractory asthma renders it challenging to untangle the interplay of the epithelium and airway smooth muscle with different types of immune cells and how these factors together determine phenotypic manifestations of severe asthma such as excessive mucus production and airway remodeling (Figure 1).³⁴ The obstacles associated with pinpointing immune modulators at the cellular level are further highlighted by emerging data on group 2 innate lymphoid (ILC2) cells, a relatively rare innate immune cell subtype that has only recently been implicated in generating substantial quantities of type 2 cytokines, such as IL-5, IL-4, and IL-13, in asthma. Thus, the nomenclature was changed from Th2, which implied production of these cytokines solely from T cells, to type 2.

TYPE 2-HIGH ASTHMA PHENOTYPES

Studies are increasingly characterizing immunological phenotypes of refractory asthma, guiding the way to targeted therapies. In a 1999 study, Wenzel et al³⁵ demonstrated that severe, corticosteroid-dependent asthma can be divided into 2 inflammatory subtypes: a type 2-high phenotype characterized by high levels of eosinophils and a type 2-low phenotype characterized by low levels of eosinophils. Each phenotype was associated with distinct physiologic and clinical characteristics.³⁵ Analysis of sputum samples from the patients in the Belgian Severe Asthma Registry showed that approximately half (55%) of severe asthma cases were eosinophilic, with the remainder having other

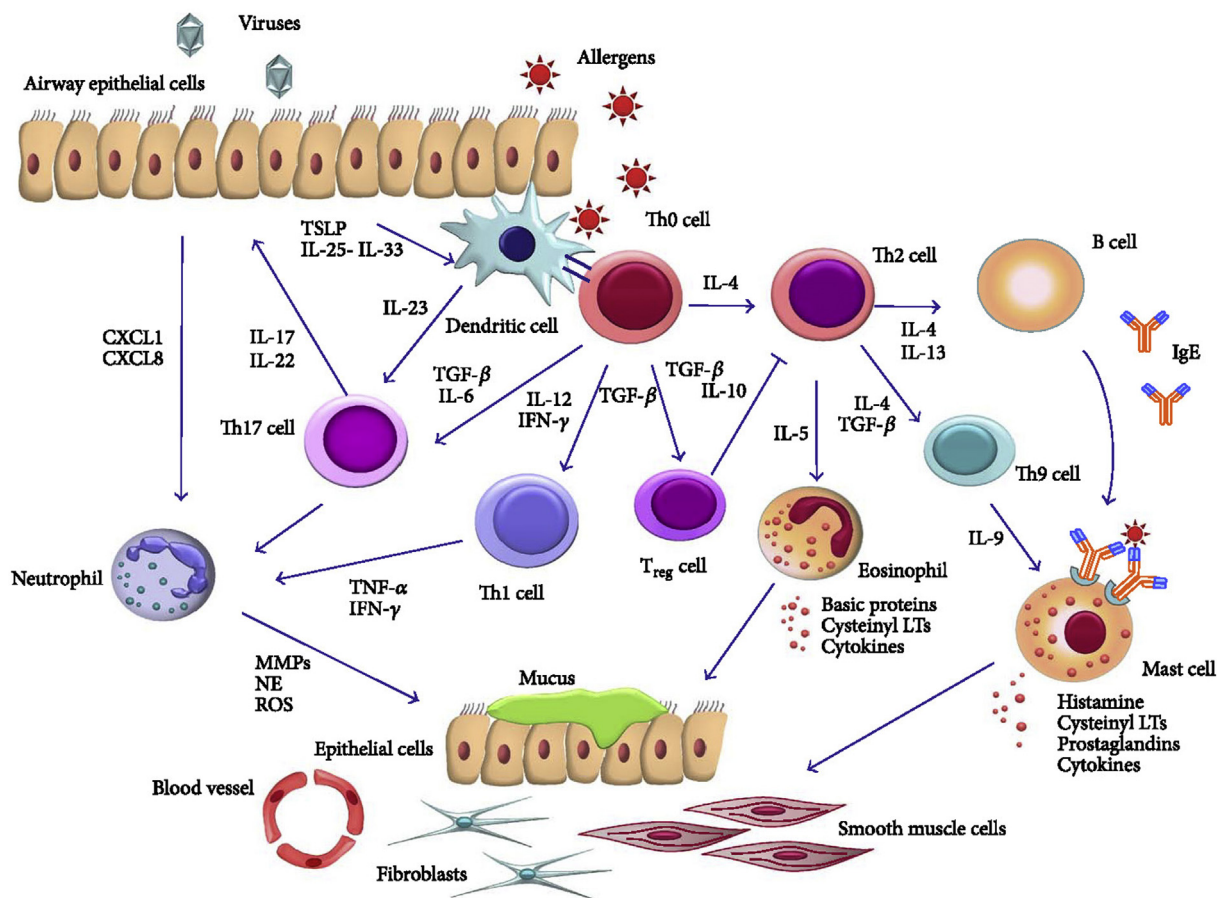


FIGURE 1. Pathobiology of airway inflammation in asthma. *LT*, Leukotriene; *MMP*, matrix metalloproteinase; *NE*, neutrophil elastase; *ROS*, reactive oxygen species; *TSLP*, thymic stromal lymphopoietin. Reproduced from Pelaia et al³⁴ under the Creative Commons Attribution License.

inflammatory phenotypes including neutrophilic (21%), paucigranulocytic (18%), and mixed granulocytic (6%).³⁶ These investigators also presented criteria defining type 2-high and type 2-low phenotypes, with the type 2-high phenotype being defined as a sputum eosinophil count of $\geq 3\%$ or the presence of both exhaled nitric oxide (eNO) ≥ 27 ppb and blood eosinophil count $\geq 188/\mu\text{L}$. By this definition, 57% of patients in the Belgian Severe Asthma Registry had eosinophilic (type 2-high) asthma and 43% had noneosinophilic (type 2-low) asthma.³⁶ It is important to note that within eosinophilic refractory asthma, the presence of eosinophils does not necessarily mean that they are the dominant effector cell type in an individual patient or that the patient's asthma is completely driven by allergic inflammation. Accordingly, giving a patient with eosinophilic asthma an anti-eosinophil biologic, such as an anti-IL-5 therapeutic, might not translate into uniform therapeutic efficacy, as demonstrated by the incomplete efficacy results in all biologic clinical trials to date.^{37,38} Instead, peripheral eosinophils should not be viewed as a biomarker that tightly predicts response in all refractory asthma but rather serves as the best discriminator of type 2 biology underpinning the disease in a given patient. Moreover, peripheral eosinophils in the blood are phenotypically distinct from eosinophils in the lung, further complicating attempts to directly correlate peripheral eosinophil counts with

therapeutic responses. This issue is compounded by a relative lack of data on eosinophil activation state and contribution to tissue cytokine levels in most studies. Awareness of these caveats in using sputum or blood eosinophil counts helps focus attention on their limitations as biomarkers for phenotyping refractory asthma.

BIOMARKERS AND PREDICTING RESPONSE TO THERAPY

To date, most of the biologic therapies that have been approved or are in development target patients with type 2-high or eosinophilic asthma. In this section, we focus our discussion on biomarkers for type 2-high asthma, which are summarized in Table I. Note that we will discuss specific biologic agents and their clinical trials in the next section, but in this section we refer to biologic therapy clinical trials as they pertain to biomarkers.

Eosinophils and fractional eNO

Much research on biomarkers has focused on eosinophils and fractional exhaled nitric oxide (FeNO). As shown in Figure 1, eosinophils clearly are key players in inflammatory immune response. FeNO is also used as a biomarker of type 2 inflammation driven by allergen exposure because epithelial stress leads

TABLE I. Summary of biomarkers

Biomarker	Treatment expected to produce a response	Associations	Comments (point of care, variability)
Blood			
Eosinophils	Anti-IL-5	Exacerbations	Easily available Significant fluctuation
	Anti-IgE	Reduced lung function	
	Anti-IL-4/IL-13	Fixed airway obstruction	
	Corticosteroids		
	CRTH2 antagonists		
Specific IgE	Anti-IgE AIT	Exacerbations Airway hyperresponsiveness (for AIT)	
Periostin	Anti-IL-13	Reduced lung function	Research type
Dipeptidyl peptidase-4 (DPP-4)		Exacerbations	Assay-dependent
Induced sputum			
Eosinophils	Anti-IL-5	Exacerbations	Currently available only in specialized centers
	ICSs		Not point of care
IL-13	Anti-IL-13	?	Research type
Exhaled breath			
FeNO	Anti-IL-5	Exacerbations	Easily available
	Anti-IgE	Reduced lung function	Point of care
	Anti-IL-13		Significant fluctuation
	ICSs		
Metabolomics (VOCs)	ICSs	?	Research type

AIT, Allergen immunotherapy; CRTH2, chemokine receptor homologous molecule expressed on Th2 lymphocytes; FeNO, fractional exhaled nitric oxide; ICSs, inhaled corticosteroids; VOCs, volatile organic compounds.

to the production of NO driven by IL-4 and IL-13.^{39,40} Exhaled NO levels increase during type 2 inflammation and often correlate with eosinophilic inflammation in the airway, with the latter being driven by IL-5.

Treatment with the anti-IL-5 biologic mepolizumab led to a decrease in blood and sputum eosinophils but not FeNO,⁴¹ which is not unexpected because FeNO is primarily driven by IL-13 and IL-4. In contrast, treatment with the anti-IL-13 biologic lebrikizumab led to a slight increase in blood eosinophils and a decrease in FeNO,⁴² as one would expect. In addition, blood eosinophil counts have been shown to predict sputum eosinophilia ($\geq 2\%$) in patients with severe asthma when blood eosinophil counts are at least 450 cells/ μL .⁴³⁻⁴⁶

Sputum eosinophils and blood eosinophils have been shown to be predictors of exacerbation. In a Belgian study, 508 patients with asthma were divided based on blood eosinophil counts ($<$ or ≥ 300 cells/ μL) and sputum eosinophils ($<$ or $\geq 3\%$).⁴⁷ High levels of both blood and sputum eosinophils were associated with both higher FeNO and a higher exacerbation rate. The exacerbation rate was 1.5 exacerbations per year for the group of patients with high blood eosinophil counts and high sputum eosinophil counts, and the exacerbation rate was even higher—3.52 exacerbations per year—for patients in this group who were on high doses of corticosteroids (>1000 $\mu\text{g/d}$ beclomethasone dipropionate). That is, these patients had the highest burden of disease, and these results point to patients who might benefit from biologic therapy. It is not understood how the eosinophils are getting into the airways from the peripheral blood or whether they are in an active state. However, it is important to point out that in this study, patients with normal blood eosinophil counts (<400 cells/ μL) but high sputum eosinophils

($\geq 3\%$) had lower airway reactivity and lower airflow limitation, but still had a relatively higher exacerbation rate compared with those without increased sputum eosinophils. Thus, blood eosinophil levels by themselves are not a sufficient biomarker in all cases but are a practical measure due to the ease of obtaining them and their reproducible methodology.

Because both FeNO and blood eosinophil counts are relatively noninvasive biomarkers, there has been much interest in whether they are reliable markers, either individually or in combination. In a study from the United States National Health and Nutrition Examination Survey stratified by blood eosinophil counts and FeNO levels, individuals with high blood eosinophil counts and high FeNO had the highest risk of current asthma, current wheeze, asthma attacks, and asthma-related ED visits.⁴⁸ That is, these 2 biomarkers identified very type 2-high patients. However, the 2 biomarkers were each independently associated with current asthma, wheeze, and asthma attacks, suggesting that each biomarker reflects a different inflammatory pathway with a separate trigger mechanism and that the 2 biomarkers cannot be used interchangeably.⁴⁸ Further, in adults with persistent asthma from the Kaiser Permanente Southern California (USA) health care system, a blood eosinophil count of at least 400 cells/ μL increased the risk of future asthma exacerbations after adjusting for potential confounding factors.⁴⁹

In the history of clinical trials of anti-IL-5 therapies (mepolizumab and reslizumab) for asthma, early studies did not include patient populations enriched for high eosinophil counts.⁵⁰ Later studies began to include only patients with high sputum eosinophil counts and eventually blood eosinophil counts, with better treatment outcomes. In a predictive model based on results from

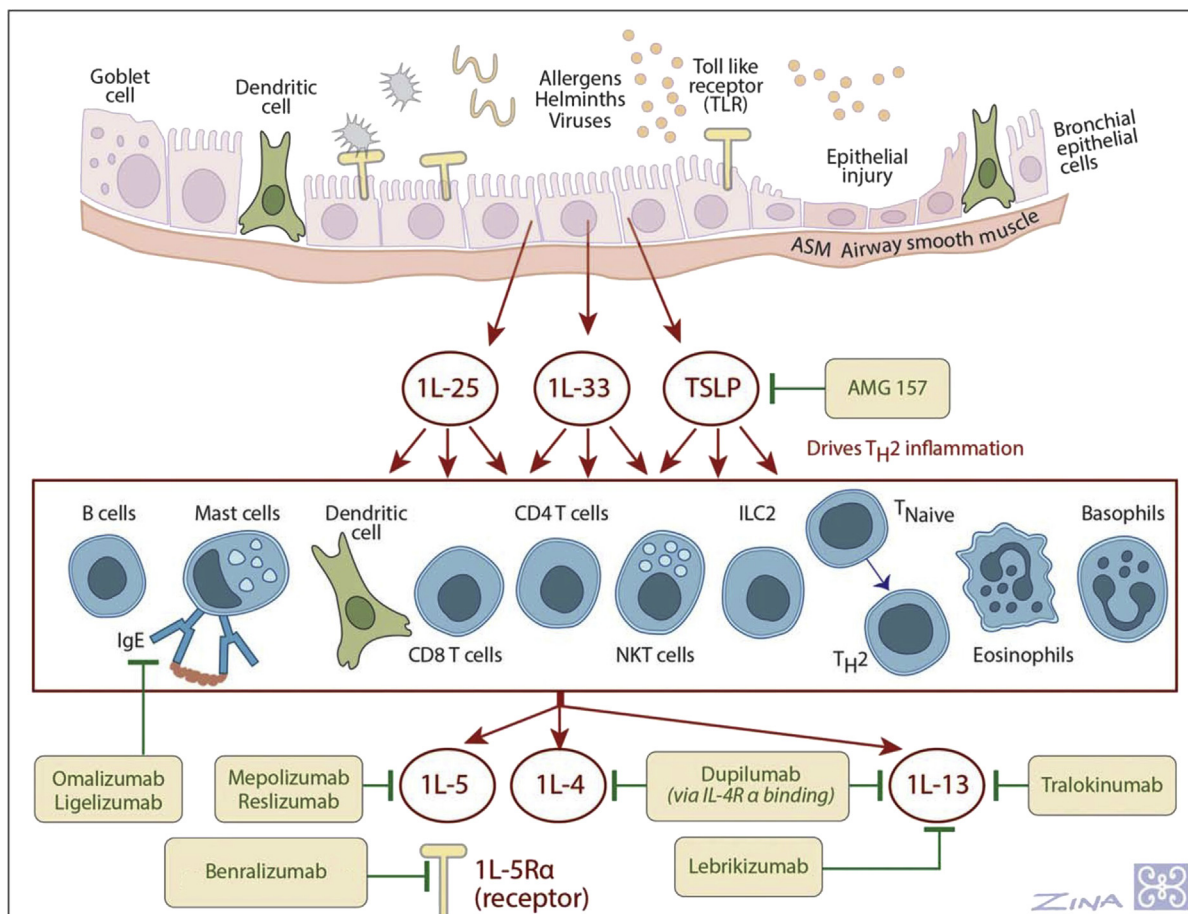


FIGURE 2. Important type 2-inflammation targets for biologic therapies. *TSLP*, Thymic stromal lymphopoietin. Adapted with permission from Mitchell et al.⁵⁷

the multicenter Dose Ranging Efficacy and Safety with Mepolizumab in severe asthma trial of mepolizumab, the reduction in exacerbation risk varied according to blood eosinophil count at baseline and the number of exacerbations in the previous year.⁵¹ That is, the greater the eosinophilic burden, the more effective the therapy, but this may have been the result of stratification alone. Interestingly, a *post hoc* analysis also found that response (decrease in exacerbation risk) to mepolizumab was better in patients who had airflow limitation caused by airway inflammation and responded to prednisolone than in patients with airway smooth muscle contraction who responded well to a bronchodilator.⁵² Identifying the mechanism of airflow limitation, therefore, could be a useful way to target individuals who would respond to treatment. Eosinophilia is a marker of susceptibility, but eosinophils do not appear to drive exacerbations in all eosinophilic patients.

Another study investigated the potential of FeNO, blood eosinophil count, and serum periostin as biomarkers of type 2 inflammation and predictors of response to treatment with omalizumab, an anti-IgE therapy.⁵³ In this study, 850 patients with uncontrolled severe persistent allergic asthma were divided into low- and high-biomarker groups for FeNO, blood eosinophils, and serum periostin at baseline. The reduction in the

exacerbation rate after 48 weeks' treatment with omalizumab was significant for the high FeNO group and the high blood eosinophil group and marginally significant for the high serum periostin group but not for any of the low-biomarker groups. Thus, these markers of type 2 inflammation appear to stratify a population of patients with refractory asthma.

Another study evaluated blood eosinophil count as a predictor of change in FEV₁ from baseline. In this study, 16 weeks of treatment with reslizumab resulted in a significant treatment effect only for patients with baseline blood eosinophil counts greater than 400 cells/ μ L.⁵⁴ However, closer examination revealed that this significant result was driven by a lower treatment effect in placebo; in addition, sample sizes were small. FEV₁ may not be an appropriate endpoint, although the original idea behind this biologic was that it would reduce exacerbation risk by improving FEV₁.

Periostin and dipeptidyl peptidase-4

Periostin, a secreted extracellular matrix protein associated with fibrosis, is correlated with airway eosinophilic inflammation,⁵⁵ and several studies have investigated periostin's potential as a noninvasive biomarker of type 2 inflammation in asthma. In the Bronchoscopic Exploratory Research Study of Biomarkers in

TABLE II. Potential biomarker targets for non-anti-IL-5 biologics*

Drug	Regulatory status	Dosing	Frequency	Route	Target	Potential biomarker target(s)
Omalizumab†	Approved 2002	150, 225, 300, or 375 mg	Q2W or Q4W	SC	IgE	IgE
Tralokinumab	Phase 3	300 mg	Q2W	SC	IL-13	DPP-4, periostin
Dupilumab	Phase 3	200 or 300 mg	Q2W or Q4W	SC	IL-4R α	Eosinophils, eNO
Lebrikizumab	Phase 3 complete‡	37.5 or 125 mg	Q4W	SC	IL-13	Sputum IL-13, periostin, DPP-4

DPP-4, Dipeptidyl peptidase-4; eNO, exhaled nitric oxide; IL-4R α , IL-4 receptor alpha; Q2W, every 2 wk; Q4W, every 4 wk; R α , receptor alpha; SC, subcutaneous.

*Patient populations between studies are not the same in regard to clinical characteristics such as exacerbations or severity.

†Data based on phase 3 studies.

‡Data inconclusive to date.

Corticosteroid-refractory Asthma, investigators compared FeNO, blood eosinophil count, serum periostin, and IgE levels with airway eosinophilia from sputum and airway tissue samples from 67 patients with uncontrolled severe asthma, and they found that serum periostin was a sensitive marker of airway eosinophilia.⁵⁵

Periostin has been demonstrated to be a biomarker of therapeutic response to lebrikizumab, an anti-IL-13 therapy.⁴² In a study of 219 adults with inadequately controlled asthma despite ICS therapy, patients with high serum periostin levels at baseline had significantly improved FEV₁ with lebrikizumab compared with placebo, whereas there was no difference in FEV₁ improvement between the lebrikizumab group and the placebo group among patients with low serum periostin at baseline.

In addition, the potential of periostin and dipeptidyl peptidase-4 (DPP-4) was evaluated in a study of tralokinumab, another anti-IL-13 therapy.⁵⁶ DPP-4, like periostin, is a protein that is upregulated by IL-13. Serum DPP-4 and periostin were elevated in a subset of patients with severe asthma. In a multicenter, phase 2b trial, 452 adults with severe asthma who had had 2 to 6 exacerbations in the previous year were assigned to receive tralokinumab or placebo. Tralokinumab improved FEV₁ in patients with elevated periostin or elevated DPP-4 but not in patients with normal levels of periostin or DPP-4; tralokinumab also reduced the exacerbation rate in patients with elevated periostin.⁵⁶

APPROVED AND PIPELINE BIOLOGIC THERAPIES

The previous section on biomarkers mentioned several biologic therapies, and in this section, we describe individual biologic therapies in more detail, focusing on those biologics that have been approved or are in phase 3 development. Figure 2 shows the type 2 inflammation targets of these biologic therapies.

Anti-IgE therapy

One anti-IgE therapeutic, omalizumab (Xolair, Genentech/Novartis, South San Francisco, CA and East Hanover, NJ), has been approved for the treatment of moderate-to-severe asthma. Omalizumab is a recombinant, humanized monoclonal IgG1K anti-IgE antibody that binds to the Fc region of IgE, preventing IgE from binding to cell-surface receptors of mast cells and basophils and thus inhibiting the release of inflammatory mediators that can cause an asthma exacerbation.⁵⁸ Omalizumab was first approved in 2002 for treating individuals aged 12 years and older with moderate or severe allergic asthma.⁵⁹ In 2016, the United States Food and Drug Administration approved its use for pediatric patients aged 6 to 12 years with moderate or severe allergic asthma. Omalizumab is administered subcutaneously (SC) every

2 or 4 weeks and is dosed according to age, treatment frequency, pretreatment IgE levels, and body weight (Table II).

Omalizumab has been shown to significantly reduce the number of exacerbations in both adults^{60,61} and children.^{62,63} In adults, omalizumab also reduced ICS dose, slightly improved FEV₁, reduced the number of asthma symptoms, and reduced the need for rescue medication.^{60,61} Similarly, in children omalizumab improved asthma control and FEV₁ and reduced hospitalization rates and ICS use.^{62,63} Omalizumab is particularly effective in reducing exacerbations in patients with high FeNO, blood eosinophils, or serum periostin.⁵³ Additional studies have supported omalizumab's efficacy.^{64,65} In a multicenter study of adolescents and adults with inadequately controlled asthma, omalizumab reduced the exacerbation rate, improved quality of life, reduced the use of controller medication, and decreased asthma symptoms.⁶⁴ Similarly, a meta-analysis of 3429 patients aged 5 to 79 years from 8 double-blind, placebo-controlled trials showed that omalizumab reduced the exacerbation rate as well as reducing ICS dose and rescue medication use.⁶⁵

Omalizumab is well tolerated. Pooled data from randomized trials indicate that adverse events (AEs) in patients who received omalizumab are similar to those in patients who received control drugs or placebo.⁶⁶ The most common AEs were nasopharyngitis, headache, respiratory tract infection, and sinusitis. Hypersensitivity reactions occurred rarely, with anaphylaxis occurring in 0.14% of patients receiving omalizumab compared with 0.07% in patients in control groups.⁶⁶ Premarket and postmarket data show that anaphylaxis generally occurs 90 to 120 minutes after omalizumab injection, and a previous history of anaphylaxis from other causes has been found to be a risk factor.⁵⁹ Omalizumab prescribing information recommends that patients be monitored for a sufficient amount of time after omalizumab injection.⁵⁹ Furthermore, although omalizumab has a boxed warning for anaphylaxis and a safety warning for malignancy,⁵⁹ the risk is small. In clinical trials, malignant neoplasms were observed in 0.5% of patients treated with omalizumab (vs 0.18% of patients who received placebo),⁶⁷ and both a pooled analysis of clinical data and a prospective post-marketing safety study (The Epidemiologic Study of Xolair) found that omalizumab was not associated with an increased risk of malignancy.^{68,69}

Anti-IL-5 therapies

To date, 2 anti-IL-5 therapies (mepolizumab and reslizumab) have been approved and 1 (benralizumab) is in phase 3 development (Table III).

Mepolizumab. Mepolizumab (Nucala, GlaxoSmithKline, Research Triangle Park, NC) is a recombinant, humanized

TABLE III. Exacerbation reduction and lung function in anti-IL-5 biologics*

Drug	Regulatory status	Dosing	Frequency	Route	Blood eosinophilia cutoff†	Exacerbation reduction rate‡	Change in FEV ₁ compared with placebo
Mepolizumab ⁷⁰	Approved 2015	100 mg	Q4W	SC	≥150 cells/μL at screening or ≥300 cells/μL in previous year	53%	98 mL
Reslizumab ⁷¹	Approved 2016	3.0 mg/kg	Q4W	IV	≥400 cells/μL	50%-59%	90-126 mL
Benralizumab ^{72,73}	Phase 3	30 mg	Q4W or Q8W§	SC	≥300 cells/μL	36% (Q4W) ⁷² 28% (Q8W) ⁷² 45% (Q4W) ⁷³ 51% (Q8W) ⁷³	125 mL (Q4W) ⁷² 116 mL (Q8W) ⁷² 106 mL (Q4W) ⁷³ 159 mL (Q8W) ⁷³

FEV₁, Forced expiratory volume in 1 s; IV, intravenous; Q4W, every 4 wk; Q8W, every 8 wk; SC, subcutaneous.

*Patient populations between studies are not the same in regard to clinical characteristics such as exacerbations or severity.

†Cutoff value for blood eosinophil counts in patient population.

‡Rate ratio vs placebo.

§First 3 doses every 4 wk.

IgG1K monoclonal anti-IL-5 antibody. Mepolizumab inhibits IL-5 from binding to the α -subunit of the IL-5 receptor complex expressed on the eosinophil cell surface, thus inhibiting the growth, differentiation, recruitment, activation, and survival of eosinophils.⁷⁴ Approved in 2015, mepolizumab is an add-on maintenance treatment for patients 12 years and older with severe eosinophilic asthma. Mepolizumab is administered subcutaneously at 100 mg every 4 weeks (Table III).

Early studies of mepolizumab did not demonstrate efficacy in terms of affecting airway hyperresponsiveness⁷⁵ or improving FEV₁,³⁷ dampening the enthusiasm for developing eosinophil-targeting therapies for asthma. However, when clinical trials focused on patients whose asthma was likely to be eosinophil dependent, anti-IL-5 therapies were shown to be effective in reducing exacerbations and decreasing the number of sputum and blood eosinophils.⁷⁶ Further studies investigated the potential of mepolizumab in treating refractory asthma guided by sputum and blood eosinophil levels.^{41,70} Mepolizumab reduced the exacerbation risk in patients with sputum eosinophilia (sputum count >3%) who had experienced at least 2 exacerbations in the previous year (relative risk [RR], 0.57; 95% confidence interval [CI], 0.32-0.92; $P = .02$).⁴¹ However, there was no significant effect of mepolizumab on asthma symptoms, FEV₁ after bronchodilator use, or hyperresponsiveness. Similarly, mepolizumab reduced the exacerbation rate in patients with recurrent exacerbations and evidence of eosinophilic inflammation (at least 150 cells/μL in peripheral blood) despite high doses of ICSs.⁷⁰ These effects seem to be independent of the atopic status of the individuals.⁷⁷ A recent meta-analysis of the treatment effects reported that mepolizumab significantly reduced the rate of exacerbations requiring hospitalization (RR, 0.49; 95% CI, 0.30-0.80; $P = .004$) and hospitalization/ED visits (RR, 0.49; 95% CI, 0.33-0.73; $P < .001$) versus placebo.⁷⁸ Studies also demonstrated that mepolizumab has OCS-sparing effects^{76,79} and improves FEV₁^{70,76} in patients with eosinophilic asthma. However, low doses of mepolizumab (100 mg SC) do not suppress sputum eosinophilia in approximately 50% of patients, and they have more modest exacerbation reduction and prednisone-sparing effects compared with patients whose sputum eosinophilia is suppressed.⁸⁰ This may be due to the inability to suppress *in situ* eosinophil poiesis that is likely to be promoted by locally derived IL-5 and IL-13 from ILC2 cells.⁸¹ The best strategy to treat such relatively poor

responders is not currently known. For example, it is unclear if these patients would respond to higher fixed doses of mepolizumab administered subcutaneously, to reslizumab administered intravenously using weight-adjusted dosing, or by targeting the IL-5 receptor.

Studies have demonstrated that mepolizumab is well tolerated. Mepolizumab's safety warnings include warnings for hypersensitivity reactions such as angioedema, bronchospasm, hypotension, urticaria, and rash, which have been observed within hours of administration of mepolizumab.⁷⁴ In addition, there is a warning against herpes zoster infection, which caused 2 serious adverse events (SAEs) in controlled clinical trials, and a caution for helminth infections. Although it is unknown whether mepolizumab affects a patient's response against parasitic infections, eosinophils may be involved in the immunological response to some helminth infections. Also, systemic or inhaled corticosteroids should be discontinued gradually under a physician's direct supervision because reduction in corticosteroid dose may be associated with systemic withdrawal symptoms or unmask conditions that had been suppressed by OCSs. Adverse reactions that occurred with at least 3% frequency among patients receiving a 100-mg SC dose of mepolizumab and occurred more frequently than in placebo groups include headache, injection site reaction, back pain, fatigue, influenza, urinary tract infection, upper abdominal pain, pruritus, eczema, and muscle spasms.

Reslizumab. Reslizumab (Cinqair, Teva Respiratory, Frazer, PA) is a humanized IgG4K monoclonal anti-IL-5 antibody that inhibits binding of IL-5 to the α -subunit of the IL-5 receptor complex expressed on the eosinophil cell surface.⁸²⁻⁸⁴ Reslizumab was approved in 2016 as an add-on maintenance treatment for patients 18 years and older with severe eosinophilic asthma. Unlike mepolizumab, reslizumab is dosed according to weight (3 mg/kg every 4 weeks) and is administered intravenously (Table III).⁸⁴ A subcutaneous product is in phase 3 trials.⁸⁵⁻⁸⁷

Reslizumab's efficacy and safety was established in a series of phase 3 randomized controlled trials, collectively known as the BREATH program.^{71,88-90} This series of trials looked at different patient populations, dosages, treatment durations, and primary endpoints. Patient populations included patients selected for elevated blood eosinophil levels (≥400 cells/μL) and patients unselected for blood eosinophil levels. These clinical trials

revealed that reslizumab improved FEV₁^{71,88,90} and reduced the exacerbation rate (RRs in 2 trials: 0.50 [95% CI, 0.37-0.67; $P < .0001$] and 0.41 [95% CI, 0.28-0.59; $P < .0001$]).⁷¹ Reslizumab had a larger effect in reducing the exacerbation frequency in patients who had a history of more frequent exacerbations, and reslizumab also increased the time to first exacerbation.⁷¹ In addition, reslizumab reduced blood eosinophil levels in patients with high blood eosinophil levels,^{71,88} improved asthma control,^{71,88,90} improved the quality of life,⁷¹ and reduced the use of rescue medications.⁹⁰ The greatest effect of reslizumab in terms of improved FEV₁, improved asthma control, and decreased rescue medication use occurred in patients with high blood eosinophil levels.^{88,90}

Pooled data from the BREATH clinical trials revealed that the incidence of AEs was lower in reslizumab-treated patients than in patients who received placebo.⁸⁴ Oropharyngeal pain was the one AE that occurred more commonly in the reslizumab group than in the placebo group, and anaphylactic reaction was the one SAE that occurred more frequently in the reslizumab group. Anaphylaxis is a boxed warning for reslizumab, but it is uncommon and considered manageable with appropriate monitoring during and after infusion. Although malignancies were observed in patients receiving reslizumab, malignancy rates were comparable with published malignancy rates. The Cinquair prescribing information also has a warning for elevated creatinine phosphokinase (CPK), which were observed more frequently among patients receiving reslizumab than in patients receiving placebo. However, these elevated CPK measurements were transient and did not cause treatment discontinuation.

Benralizumab. Benralizumab (MedImmune, Gaithersburg, MD) is an anti-IL-5 therapy in phase 3 development. It is a humanized afucosylated recombinant IgG1K monoclonal antibody that binds with high affinity to the α -subunit of the IL-5 receptor, thus inhibiting the proliferation and activation of eosinophils, while simultaneously binding to the Fc receptor Fc γ RIII α on natural killer cells, thus efficiently depleting existing eosinophils by inducing apoptosis through antibody-dependent cell-mediated cytotoxicity.⁹¹ Benralizumab is administered subcutaneously (Table III).

Early studies showed that benralizumab reduced eosinophil levels in blood, sputum, and bronchial mucosa,^{91,92} and in a subsequent phase 2b study, benralizumab (100 mg SC) reduced the exacerbation rate by 41% in adults with eosinophilic asthma who were on medium-dose or high-dose ICSs with LABAs and had had 2 to 6 exacerbations in the past year.³⁸ Benralizumab did not decrease exacerbation rates in noneosinophilic patients.³⁸ Benralizumab also resulted in significant improvements in FEV₁ and in asthma control in eosinophilic patients, noneosinophilic patients, and patients with baseline blood eosinophil counts of at least 300 cells/ μ L.³⁸ In addition, a phase 2 randomized controlled study showed that 1 dose of benralizumab reduced the exacerbation rate by 49% and the number of exacerbations resulting in hospitalization by 60% in patients who were treated in the ED for acute asthma.⁹³ Most recently, 2 phase 3 clinical trials (SIROCCO and CALIMA) have demonstrated that 56 weeks of benralizumab as an add-on therapy significantly reduces the exacerbation rate in patients with severe, uncontrolled, eosinophilic asthma (rate ratios range, 0.49-0.72).^{72,73} Benralizumab also significantly improved

prebronchodilator FEV₁ and asthma symptoms in these eosinophilic patients.^{72,73} Of note, both studies also demonstrated a reduction in annualized exacerbation rates in patients whose eosinophil levels were $<300 \mu\text{L/mL}$. In addition, dosing every 8 weeks seemed to be more effective than dosing every 4 weeks. Although this may be due to chance, it is intriguing and worth considering the effects of potential eosinophil depletion versus eosinophil normalization. Also, the treatment effects seemed to increase with disease severity. The reduction in exacerbation rates was greater in the SIROCCO trial, which generally had patients with more severe asthma, than in the CALIMA trial, which had patients with less severe forms of asthma.^{72,73}

Benralizumab appears to be well tolerated. Most AEs in early studies were mild or moderate,^{38,91,92} although in the phase 2b trial there were 7 treatment-emergent SAEs (acute cholecystitis, herpes zoster, polyarteritis nodosa, uterine leiomyoma, erythema nodosum among the 2 benralizumab groups and anaphylactic reaction and pneumonia in the placebo group).³⁸ Most AEs in the 1-dose ED study were also mild or moderate, and SAEs considered related to benralizumab were pyrexia, tachycardia, and anxiety.⁹³ In the 2 phase 3 trials, the most common AEs were worsening asthma and nasopharyngitis.^{72,73}

Anti-IL-4/13 and anti-IL-13 therapies

Agents that target the IL-4 receptor or block IL-13 are in development and offer further promise to reduce morbidity from asthma in a subset of patients (Table II).

Dupilumab. Dupilumab (Regeneron/Sanofi, Tarrytown, NY and Paris, France) is a fully human monoclonal antibody to the IL-4 receptor alpha (IL-4R α) subunit that is part of the type 2 receptor, a heterodimeric receptor complex that is activated by both IL-4 and IL-13.^{94,95} The potential to block the effects of both IL-4 and IL-13 via the IL-4R α subunit forms the basis for the development of dupilumab. IL-4 and IL-13 are important cytokines that are mainly produced by CD4⁺ Th2 cells and type 2 innate lymphoid cells but may be secreted by a host of other inflammatory cells including mast cells, basophils, and eosinophils.⁹⁶ Both IL-4 and IL-13 are increased in the airways and sputum of patients with asthma, prompting the interest into possible therapeutics targeting these cytokines.⁹⁷⁻⁹⁹ Treatment with dupilumab is being investigated in asthma^{94,95} as well as atopic dermatitis^{100,101} and chronic sinusitis with nasal polypsis.¹⁰²

Dupilumab has shown promising results with both eosinophilic and noneosinophilic asthma.^{94,95} A 12-week phase 2a trial demonstrated that subcutaneous dupilumab reduced the exacerbation rate by 87% in adult patients with moderate-to-severe, uncontrolled, eosinophilic asthma.⁹⁴ In addition, there were significant improvements in several measures of lung function and asthma control.⁹⁴ Dupilumab also resulted in a significant decrease in biomarkers of type 2 inflammation, including FeNO and IgE levels, but did not decrease blood eosinophil levels.⁹⁴ A 24-week phase 2b study, which investigated dupilumab as an add-on therapy, found that dupilumab resulted in significant improvements for patients with eosinophil levels both above and below 300 cells/ μ L with regard to the change in FEV₁ from baseline, annualized severe asthma exacerbation rates, asthma quality of life, and asthma control.⁹⁵ There was also a dose-dependent reduction in FeNO levels.⁹⁵ Based on the phase 2b

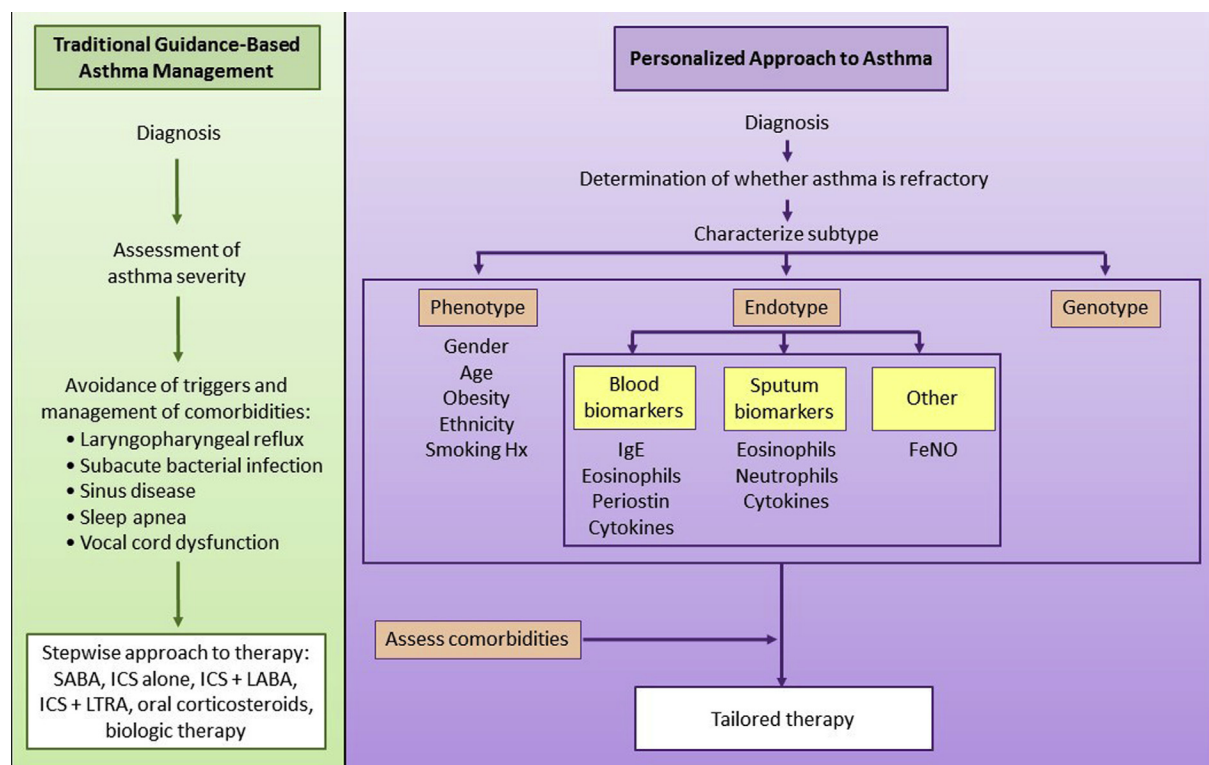


FIGURE 3. Traditional and personalized approaches to treating asthma. *FeNO*, Fractional exhaled nitric oxide; *Hx*, history; *ICS*, inhaled corticosteroid; *IgE*, immunoglobulin E; *LABA*, long-acting β -agonist; *LTRA*, leukotriene receptor antagonist; *SABA*, short-acting β -agonist. Adapted with permission from Dunn et al.⁹⁶

results, a 2-week dosing regimen has been selected for an upcoming phase 3 trial.¹⁰³

Common AEs in the phase 2a and the phase 2b studies were injection site reactions, nasopharyngitis, headache, nausea, and upper respiratory tract infection.^{94,95} A dose-response relationship with injection site reactions was suggested.⁹⁵ An unexpected rise in eosinophils was seen for patients with baseline elevated eosinophil counts, and one patient's therapy was discontinued for suspected hypereosinophilic syndrome that responded rapidly to corticosteroids.⁹⁵ Two theories have been proposed for this finding of increased eosinophilia in response to dupilumab. First, this effect could be a transient rebound elevation in eosinophil-promoting mediators such as IL-5 as a result of blocking IL-4 and IL-13.¹⁰⁴ Alternatively, because IL-4 and IL-13 recruit and facilitate eosinophil migration into tissues, inhibition of these cytokines may cause eosinophils to accumulate in the peripheral blood.¹⁰⁵ Until this issue is further elucidated, caution is advised for patients with highly elevated baseline eosinophil counts. The phase 3 trial currently in progress excludes patients with eosinophil counts of more than 1500 cells/ μ L.¹⁰³

Anti-IL-13 therapies lebrikizumab and tralokinumab. Research in anti-IL-13 therapies lebrikizumab and tralokinumab has not progressed as anticipated. Lebrikizumab (Roche, Basel, Switzerland) was in the asthma pipeline as an anti-IL-13 therapy, but its program is currently on hold after one of 2 identical phase 3 studies failed to meet its primary endpoint of reducing exacerbations in patients with severe asthma.^{106,107} However, its IL-13 target remains viable. Tralokinumab

(MedImmune, Gaithersburg, MD), another anti-IL-13 therapy, improved FEV₁ but failed to reduce exacerbation rates in a phase 2b study of patients with severe uncontrolled asthma but appeared to be effective in a subset of patients with DPP-4 levels or high periostin levels, as well as those with high sputum IL-13 levels.⁵⁶ Further research is needed to define the appropriate responder population and determine the utility of DPP-4 and periostin as biomarkers.

Other potential targets

Several other novel classes of therapy are emerging and may be potentially potent in subsets of asthma patients. These include anti-chemokine receptor homologous molecule expressed on Th2 lymphocytes,¹⁰⁸ anti-thymic stromal lymphopoietin (TSLP),¹⁰⁹ GATA3 mRNA-targeting DNazyme,¹¹⁰ anti-M1' (quilzumab; Genentech, South San Francisco, CA),^{111,112} and agents that target the IL-33,¹¹³ IL-6,¹¹⁴ and IL-17¹¹⁵ pathways. Although anti-IL-17 therapy with brodalumab (Amgen, Thousand Oaks, CA) failed to have beneficial effects across a broad range of asthma subgroups,¹¹⁵ brodalumab may be beneficial if specific biomarkers or phenotypic characteristics can identify subsets of responders.

DISCUSSION AND CONCLUSIONS

As more biologic therapies are approved, clinicians will need to consider each biologic's target and mechanism of action to determine the ideal treatment option for the individual patient, but many questions remain. For example, how do we identify these patients, and what sort of biomarkers, both current and

potential, should be used? Current guidelines call for an assessment of disease severity and stepwise approach to therapy,^{2,3} but the advent of biologic therapies calls for a new paradigm of tailored therapy based on phenotype, endotype, and possibly genotype (Figure 3).

In addition, can biologics be used in certain populations such as the exacerbation-prone individuals who do not have increased medication requirements between exacerbations? The challenge will be determining the triggers for a patient's exacerbations. Biologic therapies will clearly be beneficial for individuals with asthma, but how will they alter the progression of disease? Given that each biologic knocks out only one pathway, are multiple biologics warranted for patients in whom multiple pathways are involved? The goal is to restore the integrity of the airway in a patient and prevent exacerbations to make him or her less vulnerable to airway deterioration.

Furthermore, there is the question of who will receive these biological therapies. Will it be only those patients who are biologically difficult to treat? Or will biologics be given to a set of patients who would respond to ICSs or less aggressive therapy? These stringent, protocolized rules may be diluting the opportunity for these biologics to have a more profound effect on the progression of disease. However, there needs to be longer observations times, on the order of at least 5 years. There is also the question of whether the time to treat with these biologics should be in young children (eg, 1-5 years old) instead of adulthood (eg, 25-45 years old) to potentially modify disease susceptibility and actually prevent asthma. The problem of biologics for other disease states such as rheumatoid arthritis and inflammatory bowel disease is that the drug may only work for a short period of time and then the patient becomes tolerant to it and re-exhibits manifestations of the disease.

We recommend that patients with refractory asthma be identified using ERS/ATS guidelines¹ or similar algorithms¹² and their asthma phenotypes characterized with biomarkers, as proposed in a recent paper by Heaney et al,¹¹⁶ to assess whether patients are candidates for these novel therapies. The many novel agents for refractory asthma that are emerging are monoclonal antibodies that specifically target type 2 inflammation. However, there is also clearly a need for novel therapies that treat non-type 2 asthma patients, given that an estimated 40% to 45% of patients with refractory asthma have non-type 2/noneosinophilic asthma.³⁵ The biologic therapies discussed have potential for type 2-high patients, particularly those patients on step 5 or step 6 in the NAEPP EPR-3 guidelines.³ Although perhaps someday biologic therapies may be given to patients with less severe asthma, there are no data supporting their use in this population, and at the present time, the cost is likely prohibitive.

A variety of biomarkers have been proposed in the hopes that biologic therapies can be tailored to individual asthma phenotypes. Each biomarker has its pros and cons.¹¹⁷ Sputum eosinophilia correlates with airway inflammation, decreased FEV₁, and increased bronchial hyperresponsiveness, and treatment response; however, it can be difficult to obtain. Blood eosinophil counts are easier to obtain, but they are neither sensitive nor specific for asthma. Although blood eosinophil counts are helpful for stratifying type 2-high versus type 2-low phenotypes, there is no evidence that blood eosinophil counts are useful for adjusting ICSs to improve outcomes, and the sensitivity of blood eosinophil levels is less than that of airway eosinophilia. Total IgE, specific IgE, and FeNO are easy to obtain and correlate with

airway eosinophilic inflammation and atopic asthma. However, IgE is not specific for all asthma types, and FeNO is not specific to lower airway inflammation. Serum periostin is a sensitive indicator of eosinophilic and type 2-mediated airway inflammation in persistent uncontrolled asthma, but it is not readily available. In addition, the clinical utility of serum periostin, sputum eosinophil levels, biopsy (lavage) eosinophil levels, and tissue eosinophil levels as measures of airway eosinophilia has not yet been fully elucidated.⁵⁵ A similar problem arises with FeNO and blood eosinophil counts.^{41,42} DPP-4, although promising, may also prove to be a specific indicator of type 2-mediated inflammation, but it is not readily available at this time.

Thus, phenotyping patients to determine the best therapy is still in its infancy, and further research targeting predictors of response to treatment is needed. This will require not only a panel of biomarkers and understanding the type 2 inflammatory pathway, but also determining the cause of exacerbations in unique patient populations. One individual biomarker is not better than the others, but each biomarker provides the clinician with useful information that collectively may help in deciding the best treatment for that patient. Ultimately, we need to develop a protocolized approach for specialists as well as guidance for primary care providers on when to refer a patient to a specialist or a center of excellence, where the patient could be considered eligible for a biologic therapy.

Where does this leave us? It is unlikely that there will be a single biomarker that tells us everything. We must understand the biomarkers pathophysiologically and synthesize the information from several biomarkers to help clinicians make decisions as these new therapies begin to reach their practice. An attempt at an algorithmic approach to general asthma phenotypes and treatment has been suggested by Chung,¹¹⁸ but this approach is premature and may prove impractical given that some of the suggested treatments have had their development stalled (eg, anti-IL-13). In addition, some of the proposed phenotypes (eg, corticosteroid insensitive, type 2-low, noneosinophilic, or neutrophilic) still require further investigation to accurately characterize potential endotypes. Despite these limitations, the aforementioned type 2-high biomarker-driven therapies are a significant step forward in personalized asthma care.

Because asthma is an airway disorder, we should study the airway in patients with refractory asthma to determine phenotypes and endotypes and link those phenotypes and endotypes to directed therapies. This approach can be invasive (eg, bronchoscopy) but could be helpful in understanding asthma phenotypes and endotypes. This has been done in a study of patients with refractory asthma as defined by ERS/ATS criteria.¹¹⁹ In this study, 34 patients with difficult-to-treat, refractory asthma were phenotyped using a variety of methods, including fiber-optic bronchoscopy with visual scoring of the upper and lower airways, bronchoalveolar lavage, endobronchial biopsy, and brush. Bronchoscopic evaluation defined 5 mutually exclusive phenotypes: gastroesophageal reflux, subacute bacterial infection, tissue eosinophilia, combination, and nonspecific. Using precision medicine with directed therapy, patients improved in several outcome measures, including asthma control, lung function, and reduction in OCS use.

Patients with refractory asthma have an unmet need, and treatment is complicated by heterogeneity within the clinical syndrome of asthma. Treatment will need to be individualized based on each patient's endotype, but to date we know very little

about refractory asthma endotypes, how to identify these endotypes, and what treatment to use for a given endotype. For some patients, we may not currently have available appropriate, effective therapies. Biologic therapies have an immense potential to be part of refractory asthma treatment, and with the appropriate guidance, the clinician should feel comfortable choosing the right therapy for his or her patient. Unfortunately, which therapy to choose from at this time is limited to type 2-high patients, while further characterization is required to delineate therapy for type 2-low patients.

Among the currently approved biomarker therapies described above (omalizumab, mepolizumab, and reslizumab), the decision of which therapy to initiate depends on a combination of atopic history, biomarker presence (ie, IgE with or without elevated blood eosinophil levels vs other potential biomarkers), prior treatment response (ie, prior biologic failure), specific goals of the patient or clinician (eg, reduce exacerbations, improve lung function, reduce medication burden), and which side effect profile is most tolerable to the patient. Fortunately, these therapies appear to be safe and tolerable. Looking forward, as therapies emerge we will gain a better understanding of what defines treatment response with more precision as well as modulation of dosing intervals and duration. In addition, as comfort is gained with treatment with one biologic, the next step will be to study some of these drugs in combination to concurrently block multiple pathways in hopes of obtaining greater efficacy.

Many questions remain to be answered on how to better characterize a patient's endotype and phenotype as well as how to choose which therapy is most appropriate for the individual patient. Despite our recognized knowledge gaps, when treating a patient with refractory asthma, an individualized approach to characterize the patient is the first step and remains a crucial part of the clinician's evaluation. With recent and imminent approvals of different biologic therapies, an individualized treatment plan for this difficult to manage population is now within reach.

Acknowledgments

The authors thank Elise Eller, PhD, for her assistance in preparing this article. The National Jewish Health Office of Professional Education, particularly Ayndrea Patterson, Sarah Meadows, MS, CHCP, and Andrea Harshman, MHA, CHCP, were instrumental in the development of this article as part of a multimodal educational program.

REFERENCES

- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343-73.
- Global Initiative for Asthma (GINA). Global Strategy for Asthma Management and Prevention. Updated 2016. Available from: <http://ginasthma.org/2016-gina-report-global-strategy-for-asthma-management-and-prevention/>. Accessed October 24, 2016.
- National Asthma Education and Prevention Program. Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma. Bethesda, MD: National Heart, Lung, and Blood Institute (US). Available from: <http://www.nhlbi.nih.gov/health-pro/guidelines/current/asthma-guidelines/full-report>; 2007. Accessed December 5, 2015.
- Chung KF, Godard P, Adelroth E, Ayres J, Barnes N, Barnes P, et al. Difficult/therapy-resistant asthma: the need for an integrated approach to define clinical phenotypes, evaluate risk factors, understand pathophysiology and find novel therapies. ERS Task Force on Difficult/Therapy-Resistant Asthma. European Respiratory Society. *Eur Respir J* 1999;13:1198-208.
- Proceedings of the ATS workshop on refractory asthma. current understanding, recommendations, and unanswered questions. American Thoracic Society. *Am J Respir Crit Care Med* 2000;162:2341-51.
- The ENFUMOSA cross-sectional European multicentre study of the clinical phenotype of chronic severe asthma. European Network for Understanding Mechanisms of Severe Asthma. *Eur Respir J* 2003;22:470-7.
- Dolan CM, Fraher KE, Bleecker ER, Borish L, Chipps B, Hayden ML, et al. Design and baseline characteristics of the epidemiology and natural history of asthma: Outcomes and Treatment Regimens (TENOR) study: a large cohort of patients with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2004;92:32-9.
- Chanez P, Wenzel SE, Anderson GP, Anto JM, Bel EH, Boulet LP, et al. Severe asthma in adults: what are the important questions? *J Allergy Clin Immunol* 2007;119:1337-48.
- Taylor DR, Bateman ED, Boulet LP, Boushey HA, Busse WW, Casale TB, et al. A new perspective on concepts of asthma severity and control. *Eur Respir J* 2008;32:545-54.
- Bousquet J, Mantzouranis E, Cruz AA, Ait-Khaled N, Baena-Cagnani CE, Bleecker ER, et al. Uniform definition of asthma severity, control, and exacerbations: document presented for the World Health Organization Consultation on Severe Asthma. *J Allergy Clin Immunol* 2010;126:926-38.
- Hedlin G, Bush A, Lodrup Carlsen K, Wennergren G, De Benedictis FM, Melen E, et al. Problematic severe asthma in children, not one problem but many: a GA²LEN initiative. *Eur Respir J* 2010;36:196-201.
- Bel EH, Sousa A, Fleming L, Bush A, Chung KF, Versnel J, et al. Diagnosis and definition of severe refractory asthma: an international consensus statement from the Innovative Medicine Initiative (IMI). *Thorax* 2011;66:910-7.
- Hekking PP, Wener RR, Amelink M, Zwiderman AH, Bouvy ML, Bel EH. The prevalence of severe refractory asthma. *J Allergy Clin Immunol* 2015;135:896-902.
- Taylor WR, Newacheck PW. Impact of childhood asthma on health. *Pediatrics* 1992;90:657-62.
- Vollmer WM, Markson LE, O'Connor E, Frazier EA, Berger M, Buist AS. Association of asthma control with health care utilization: a prospective evaluation. *Am J Respir Crit Care Med* 2002;165:195-9.
- Tough SC, Hessel PA, Ruff M, Green FH, Mitchell I, Butt JC. Features that distinguish those who die from asthma from community controls with asthma. *J Asthma* 1998;35:657-65.
- Antonicevici L, Bucca C, Neri M, De Benedetto F, Sabbatani P, Bonifazi F, et al. Asthma severity and medical resource utilisation. *Eur Respir J* 2004;23:723-9.
- Jarjour NN, Erzurum SC, Bleecker ER, Calhoun WJ, Castro M, Comhair SA, et al. Severe asthma: lessons learned from the National Heart, Lung, and Blood Institute Severe Asthma Research Program. *Am J Respir Crit Care Med* 2012;185:356-62.
- Szeffler SJ, Zeiger RS, Haselkorn T, Mink DR, Kamath TV, Fish JE, et al. Economic burden of impairment in children with severe or difficult-to-treat asthma. *Ann Allergy Asthma Immunol* 2011;107:110-119.e1.
- Phelan PD, Robertson CF, Olinsky A. The Melbourne Asthma Study: 1964-1999. *J Allergy Clin Immunol* 2002;109:189-94.
- Yunginger JW, Reed CE, O'Connell EJ, Melton LJ III, O'Fallon WM, Silverstein MD. A community-based study of the epidemiology of asthma. Incidence rates, 1964-1983. *Am Rev Respir Dis* 1992;146:888-94.
- Halder P, Pavord ID, Shaw DE, Berry MA, Thomas M, Brightling CE, et al. Cluster analysis and clinical asthma phenotypes. *Am J Respir Crit Care Med* 2008;178:218-24.
- Schatz M, Hsu JW, Zeiger RS, Chen W, Dorenbaum A, Chipps BE, et al. Phenotypes determined by cluster analysis in severe or difficult-to-treat asthma. *J Allergy Clin Immunol* 2014;133:1549-56.
- Newby C, Heaney LG, Menzies-Gow A, Niven RM, Mansur A, Bucknall C, et al. Statistical cluster analysis of the British Thoracic Society Severe refractory Asthma Registry: clinical outcomes and phenotype stability. *PLoS One* 2014;9:e102987.
- Fitzpatrick AM, Stephenson ST, Brown MR, Nguyen K, Douglas S, Brown LA. Systemic corticosteroid responses in children with severe asthma: phenotypic and endotypic features [e-pub ahead of print]. *J Allergy Clin Immunol Pract* 2016. <http://dx.doi.org/10.1016/j.jaip.2016.08.001>.
- Chipps BE, Zeiger RS, Borish L, Wenzel SE, Yegin A, Hayden ML, et al. Key findings and clinical implications from The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2012;130:332-342.e10.
- Miller MK, Lee JH, Miller DP, Wenzel SE. TENOR Study Group. Recent asthma exacerbations: a key predictor of future exacerbations. *Respir Med* 2007;101:481-9.
- Haselkorn T, Fish JE, Zeiger RS, Szeffler SJ, Miller DP, Chipps BE, et al. Consistently very poorly controlled asthma, as defined by the impairment

- domain of the Expert Panel Report 3 guidelines, increases risk for future severe asthma exacerbations in The Epidemiology and Natural History of Asthma: Outcomes and Treatment Regimens (TENOR) study. *J Allergy Clin Immunol* 2009;124:895-902.e1-4.
29. Bateman ED, Buhl R, O'Byrne PM, Humbert M, Reddel HK, Sears MR, et al. Development and validation of a novel risk score for asthma exacerbations: the risk score for exacerbations. *J Allergy Clin Immunol* 2015;135:1457-1464.e4.
30. Denlinger LC, Phillips BR, Ramratnam S, Ross K, Bhakta NR, Cardet JC, et al. Inflammatory and co-morbid features of patients with severe asthma and frequent exacerbations. *Am J Respir Crit Care Med* 2017;195:302-13.
31. Shaw DE, Sousa AR, Fowler SJ, Fleming LJ, Roberts G, Corfield J, et al. Clinical and inflammatory characteristics of the European U-BIOPRED adult severe asthma cohort. *Eur Respir J* 2015;46:1308-21.
32. Fleming L, Murray C, Bansal AT, Hashimoto S, Bisgaard H, Bush A, et al. The burden of severe asthma in childhood and adolescence: results from the paediatric U-BIOPRED cohorts. *Eur Respir J* 2015;46:1322-33.
33. Wilson SJ, Ward JA, Sousa AR, Corfield J, Bansal AT, De Meulder B, et al. Severe asthma exists despite suppressed tissue inflammation: findings of the U-BIOPRED study. *Eur Respir J* 2016;48:1307-19.
34. Pelaia G, Vatrella A, Busceti MT, Gallelli L, Calabrese C, Terracciano R, et al. Cellular mechanisms underlying eosinophilic and neutrophilic airway inflammation in asthma. *Mediators Inflamm* 2015;2015:879783.
35. Wenzel SE, Schwartz LB, Langmack EL, Halliday JL, Trudeau JB, Gibbs RL, et al. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001-8.
36. Schleich F, Brusselle G, Louis R, Vandenplas O, Michils A, Pilette C, et al. Heterogeneity of phenotypes in severe asthmatics. The Belgian Severe Asthma Registry (BSAR). *Respir Med* 2014;108:1723-32.
37. Flood-Page P, Swenson C, Faerman I, Matthews J, Williams M, Brannick L, et al. A study to evaluate safety and efficacy of mepolizumab in patients with moderate persistent asthma. *Am J Respir Crit Care Med* 2007;176:1062-71.
38. Castro M, Wenzel SE, Bleecker ER, Pizzichini E, Kuna P, Busse WW, et al. Benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, versus placebo for uncontrolled eosinophilic asthma: a phase 2b randomised dose-ranging study. *Lancet Respir Med* 2014;2:879-90.
39. Yates DH. Role of exhaled nitric oxide in asthma. *Immunol Cell Biol* 2001;79:178-90.
40. Alving K, Malinowski A. Basic aspects of exhaled nitric oxide. *Eur Respir Mon* 2010;48:1-31.
41. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;360:973-84.
42. Corren J, Lemanske RF, Hanania NA, Korenblat PE, Parsey MV, Arron JR, et al. Lebrikizumab treatment in adults with asthma. *N Engl J Med* 2011;365:1088-98.
43. Farooqui N, Khan BQ, Wan JY, Lieberman P. Blood eosinophils as markers of inflammation in asthma. *Ann Allergy Asthma Immunol* 2009;103(Suppl 3):A56-7.
44. van Veen IH, ten Brinke A, Gauw SA, Sterk PJ, Rabe KF, Bel EH. Consistency of sputum eosinophilia in difficult-to-treat asthma: a 5-year follow-up study. *J Allergy Clin Immunol* 2009;124:615-7. 7.e1-2.
45. Westerhof GA, Korevaar DA, Amelink M, de Nijs SB, de Groot JC, Wang J, et al. Biomarkers to identify sputum eosinophilia in different adult asthma phenotypes. *Eur Respir J* 2015;46:688-96.
46. Fowler SJ, Tavernier G, Niven R. High blood eosinophil counts predict sputum eosinophilia in patients with severe asthma. *J Allergy Clin Immunol* 2015;135:822-824.e2.
47. Schleich FN, Chevremont A, Paulus V, Henket M, Manise M, Seidel L, et al. Importance of concomitant local and systemic eosinophilia in uncontrolled asthma. *Eur Respir J* 2014;44:97-108.
48. Malinowski A, Fonseca JA, Jacinto T, Alving K, Janson C. Exhaled nitric oxide levels and blood eosinophil counts independently associate with wheeze and asthma events in National Health and Nutrition Examination Survey subjects. *J Allergy Clin Immunol* 2013;132:821-827.e1-5.
49. Zeiger RS, Schatz M, Li Q, Chen W, Khatry DB, Gossage D, et al. High blood eosinophil count is a risk factor for future asthma exacerbations in adult persistent asthma. *J Allergy Clin Immunol Pract* 2014;2:741-50.
50. Hargreave FE, Nair P. Point: is measuring sputum eosinophils useful in the management of severe asthma? Yes. *Chest* 2011;139:1270-3.
51. Pavord ID, Korn S, Howarth P, Bleecker ER, Buhl R, Keene ON, et al. Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 2012;380:651-9.
52. Pavord ID, Haldar P, Bradding P, Wardlaw AJ. Mepolizumab in refractory eosinophilic asthma. *Thorax* 2010;65:370.
53. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;187:804-11.
54. United States Food and Drug Administration (FDA) Briefing Document. BLA 761033: Reslizumab for intravenous injection to reduce exacerbations, relieve symptoms, and improve lung function in adults and adolescents (12 years of age and above) with asthma and elevated blood eosinophils who are inadequately controlled on inhaled corticosteroids; 2015. Available from: <http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Pulmonary-AllergyAdvisoryCommittee/UCM475759.pdf>. Accessed July 25, 2016.
55. Jia G, Erickson RW, Choy DF, Mosesova S, Wu LC, Solberg OD, et al. Periostin is a systemic biomarker of eosinophilic airway inflammation in asthmatic patients. *J Allergy Clin Immunol* 2012;130:647-654.e10.
56. Brightling CE, Chaney P, Leigh R, O'Byrne PM, Korn S, She D, et al. Efficacy and safety of tralokinumab in patients with severe uncontrolled asthma: a randomised, double-blind, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2015;3:692-701.
57. Mitchell PD, El-Gammal AI, O'Byrne PM. Emerging monoclonal antibodies as targeted innovative therapeutic approaches to asthma. *Clin Pharmacol Ther* 2016;99:38-48.
58. Strunk RC, Bloomberg GR. Omalizumab for asthma. *N Engl J Med* 2006;354:2689-95.
59. Xolair [prescribing information]. South San Francisco, Calif: Genentech/Novartis; 2016. Available from: http://www.gene.com/download/pdf/xolair_prescribing.pdf. Accessed July 28, 2016.
60. Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184-90.
61. Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254-61.
62. Deschildre A, Marguet C, Salleron J, Pin I, Rittie JL, Derelle J, et al. Add-on omalizumab in children with severe allergic asthma: a 1-year real life survey. *Eur Respir J* 2013;42:1224-33.
63. Deschildre A, Marguet C, Langlois C, Pin I, Rittie JL, Derelle J, et al. Real-life long-term omalizumab therapy in children with severe allergic asthma. *Eur Respir J* 2015;46:856-9.
64. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;154:573-82.
65. Rodrigo GJ, Neffen H, Castro-Rodriguez JA. Efficacy and safety of subcutaneous omalizumab vs placebo as add-on therapy to corticosteroids for children and adults with asthma: a systematic review. *Chest* 2011;139:28-35.
66. Humbert M, Busse W, Hanania NA, Lowe PJ, Canvin J, Erpenbeck VJ, et al. Omalizumab in asthma: an update on recent developments. *J Allergy Clin Immunol Pract* 2014;2:525-536.e1.
67. Corren J, Casale TB, Lanier B, Buhl R, Holgate S, Jimenez P. Safety and tolerability of omalizumab. *Clin Exp Allergy* 2009;39:788-97.
68. Busse W, Buhl R, Fernandez Vidaurre C, Blogg M, Zhu J, Eisner MD, et al. Omalizumab and the risk of malignancy: results from a pooled analysis. *J Allergy Clin Immunol* 2012;129:983-989.e6.
69. Long A, Rahmaoui A, Rothman KJ, Guinan E, Eisner M, Bradley MS, et al. Incidence of malignancy in patients with moderate-to-severe asthma treated with or without omalizumab. *J Allergy Clin Immunol* 2014;134:560-567.e4.
70. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;371:1198-207.
71. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;3:355-66.
72. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;388:2128-41.
73. Bleecker ER, FitzGerald JM, Chaney P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;388:2115-27.
74. Nucala [prescribing information]. Research Triangle Park, NC: GlaxoSmithKline; 2015. Available from: <https://www.gsksource.com/>

- pharma/content/dam/GlaxoSmithKline/US/en/Prescribing_Information/Nucala/pdf/NUCALA-PI-PIL.PDF. Accessed May 30, 2016.
75. Leckie MJ, ten Brinke A, Khan J, Diamant Z, O'Connor BJ, Walls CM, et al. Effects of an interleukin-5 blocking monoclonal antibody on eosinophils, airway hyper-responsiveness, and the late asthmatic response. *Lancet* 2000; 356:2144-8.
 76. Nair P, Pizzichini MM, Kjarsgaard M, Inman MD, Efthimiadis A, Pizzichini E, et al. Mepolizumab for prednisone-dependent asthma with sputum eosinophilia. *N Engl J Med* 2009;360:985-93.
 77. Ortega H, Chupp G, Bardin P, Bourdin A, Garcia G, Hartley B, et al. The role of mepolizumab in atopic and nonatopic severe asthma with persistent eosinophilia. *Eur Respir J* 2014;44:239-41.
 78. Yancey SW, Ortega HG, Keene ON, Mayer B, Gunsoy NB, Brightling CE, et al. Meta-analysis of asthma-related hospitalization in mepolizumab studies of severe eosinophilic asthma [e-pub ahead of print]. *J Allergy Clin Immunol* 2016. <http://dx.doi.org/10.1016/j.jaci.2016.08.008>.
 79. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;371:1189-97.
 80. Sehmi R, Smith SG, Kjarsgaard M, Radford K, Boulet LP, Lemiere C, et al. Role of local eosinophilopoietic processes in the development of airway eosinophilia in prednisone-dependent severe asthma. *Clin Exp Allergy* 2016; 46:793-802.
 81. Smith SG, Chen R, Kjarsgaard M, Huang C, Oliveria JP, O'Byrne PM, et al. Increased numbers of activated group 2 innate lymphoid cells in the airways of patients with severe asthma and persistent airway eosinophilia. *J Allergy Clin Immunol* 2016;137:75-86.e8.
 82. Egan RW, Athwal D, Bodmer MW, Carter JM, Chapman RW, Chou CC, et al. Effect of Sch 55700, a humanized monoclonal antibody to human interleukin-5, on eosinophilic responses and bronchial hyperreactivity. *Arzneimittelforschung* 1999;49:779-90.
 83. Zhang J, Kuvelkar R, Murgolo NJ, Taremi SS, Chou CC, Wang P, et al. Mapping and characterization of the epitope(s) of Sch 55700, a humanized mAb, that inhibits human IL-5. *Int Immunol* 1999;11:1935-44.
 84. Cinqair [prescribing information]. Frazer, Pa: Teva Respiratory, LLC; 2016. Available from: <http://www.cinqair.com/pdf/PrescribingInformation.pdf>. Accessed October 21, 2016.
 85. An efficacy and safety study of reslizumab subcutaneous in patients with oral corticosteroid dependent asthma and elevated blood eosinophils. Available from: <https://clinicaltrials.gov/ct2/show/NCT02501629>. Updated October 5, 2016. Accessed October 26, 2016.
 86. Study of reslizumab in patients with uncontrolled asthma and elevated blood eosinophils. Available from: <https://clinicaltrials.gov/ct2/show/NCT02452190>. Updated September 4, 2016. Accessed October 26, 2016.
 87. Anti-interleukin-5 (IL5) monoclonal antibody (mAb) in prednisone-dependent eosinophilic asthma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02559791>. Updated February 9, 2016. Accessed October 26, 2016.
 88. Bjerner L, Lemiere C, Maspero J, Ciesielska M, O'Brien C, Sangrilli J. A randomized phase 3 study of the efficacy and safety of reslizumab in subjects with asthma with elevated eosinophils. *Eur Respir J* 2014;44:P299.
 89. Maspero J, Bjerner L, Lemiere C, Sangrilli J. A randomized phase 3 study assessing patient-reported outcomes and safety of reslizumab in patients with asthma with elevated eosinophils. *Ann Allergy Asthma Immunol* 2014;113:A21.
 90. Corren J, Weinstein S, Janka L, O'Brien C, Sangrilli J. A randomized phase 3 study of reslizumab efficacy in relation to blood eosinophil levels in patients with moderate to severe asthma. *Eur Respir J* 2014;44(Suppl 58):4673.
 91. Busse WW, Katial R, Gossage D, Sari S, Wang B, Kolbeck R, et al. Safety profile, pharmacokinetics, and biologic activity of MEDI-563, an anti-IL-5 receptor alpha antibody, in a phase I study of subjects with mild asthma. *J Allergy Clin Immunol* 2010;125:1237-1244.e2.
 92. Laviolette M, Gossage DL, Gauvreau G, Leigh R, Olivenstein R, Katial R, et al. Effects of benralizumab on airway eosinophils in asthmatic patients with sputum eosinophilia. *J Allergy Clin Immunol* 2013;132:1086-1096.e5.
 93. Nowak RM, Parker JM, Silverman RA, Rowe BH, Smithline H, Khan F, et al. A randomized trial of benralizumab, an anti-interleukin 5 receptor alpha monoclonal antibody, after acute asthma. *Am J Emerg Med* 2015;33:14-20.
 94. Wenzel S, Ford L, Pearlman D, Spector S, Sher L, Skobieranda F, et al. Dupilumab in persistent asthma with elevated eosinophil levels. *N Engl J Med* 2013;368:2455-66.
 95. Wenzel S, Castro M, Corren J, Maspero J, Wang L, Zhang B, et al. Dupilumab efficacy and safety in adults with uncontrolled persistent asthma despite use of medium-to-high-dose inhaled corticosteroids plus a long-acting beta2 agonist: a randomised double-blind placebo-controlled pivotal phase 2b dose-ranging trial. *Lancet* 2016;388:31-44.
 96. Dunn RM, Wechsler ME. Anti-interleukin therapy in asthma. *Clin Pharmacol Ther* 2015;97:55-65.
 97. Saha SK, Berry MA, Parker D, Siddiqui S, Morgan A, May R, et al. Increased sputum and bronchial biopsy IL-13 expression in severe asthma. *J Allergy Clin Immunol* 2008;121:685-91.
 98. Humbert M, Durham SR, Ying S, Kimmitt P, Barkans J, Assoufi B, et al. IL-4 and IL-5 mRNA and protein in bronchial biopsies from patients with atopic and nonatopic asthma: evidence against "intrinsic" asthma being a distinct immunopathologic entity. *Am J Respir Crit Care Med* 1996;154:1497-504.
 99. Maes T, Joos GF, Brusselle GG. Targeting interleukin-4 in asthma: lost in translation? *Am J Respir Cell Mol Biol* 2012;47:261-70.
 100. Beck LA, Thaci D, Hamilton JD, Graham NM, Bieber T, Rocklin R, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med* 2014;371:130-9.
 101. Thaci D, Simpson EL, Beck LA, Bieber T, Blauvelt A, Papp K, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet* 2016;387:40-52.
 102. Bachert C, Mannent L, Naclerio RM, Mullol J, Ferguson BJ, Gevaert P, et al. Effect of subcutaneous dupilumab on nasal polyp burden in patients with chronic sinusitis and nasal polyposis: a randomized clinical trial. *JAMA* 2016; 315:469-79.
 103. A double blind, placebo-controlled, parallel group study to evaluate the efficacy and safety of dupilumab in patients with persistent asthma. Available from: <https://clinicaltrials.gov/ct2/show/NCT02414854>. Updated August 2, 2016. Accessed August 5, 2016.
 104. Chung KF. Dupilumab: a potential new treatment for severe asthma. *Lancet* 2016;388:3-4.
 105. Darveaux J, Busse WW. Biologics in asthma—the next step toward personalized treatment. *J Allergy Clin Immunol Pract* 2015;3:152-60. quiz 61.
 106. Hanania NA, Korenblat P, Chapman KR, Bateman ED, Kopecky P, Paggiaro P, et al. Efficacy and safety of lebrikizumab in patients with uncontrolled asthma (LAVOLTA I and LAVOLTA II): replicate, phase 3, randomised, double-blind, placebo-controlled trials. *Lancet Respir Med* 2016; 4:781-96.
 107. Roche provides update on two identical phase III studies of lebrikizumab in people with severe asthma; 2016. Available from: <http://www.roche.com/investors/updates/inv-update-2016-02-29.htm>. Accessed October 25, 2016.
 108. Hall IP, Fowler AV, Gupta A, Tetzlaff K, Nivens MC, Sarno M, et al. Efficacy of BI 671800, an oral CRTH2 antagonist, in poorly controlled asthma as sole controller and in the presence of inhaled corticosteroid treatment. *Pulm Pharmacol Ther* 2015;32:37-44.
 109. Gauvreau GM, O'Byrne PM, Boulet LP, Wang Y, Cockcroft D, Bigler J, et al. Effects of an anti-TSLP antibody on allergen-induced asthmatic responses. *N Engl J Med* 2014;370:2102-10.
 110. Krug N, Hohlfield JM, Kirsten AM, Kornmann O, Beeh KM, Kappeler D, et al. Allergen-induced asthmatic responses modified by a GATA3-specific DNase. *N Engl J Med* 2015;372:1987-95.
 111. Gauvreau GM, Harris JM, Boulet LP, Scheerens H, Fitzgerald JM, Putnam WS, et al. Targeting membrane-expressed IgE B cell receptor with an antibody to the M1 prime epitope reduces IgE production. *Sci Transl Med* 2014;6:243ra85.
 112. Harris JM, Maciuga R, Bradley MS, Cabanski CR, Scheerens H, Lim J, et al. A randomized trial of the efficacy and safety of quilizumab in adults with inadequately controlled allergic asthma. *Respir Res* 2016;17:29.
 113. Nabe T. Interleukin (IL)-33: new therapeutic target for atopic diseases. *J Pharmacol Sci* 2014;126:85-91.
 114. Chu DK, Al-Garawi A, Llop-Guevara A, Pillai RA, Radford K, Shen P, et al. Therapeutic potential of anti-IL-6 therapies for granulocytic airway inflammation in asthma. *Allergy Asthma Clin Immunol* 2015;11:14.
 115. Busse WW, Holgate S, Kerwin E, Chon Y, Feng J, Lin J, et al. Randomized, double-blind, placebo-controlled study of brodalumab, a human anti-IL-17 receptor monoclonal antibody, in moderate to severe asthma. *Am J Respir Crit Care Med* 2013;188:1294-302.
 116. Heaney LG, Djukanovic R, Woodcock A, Walker S, Matthews JG, Pavord ID, et al. Research in progress: Medical Research Council United Kingdom Refractory Asthma Stratification Programme (RASP-UK). *Thorax* 2016;71:187-9.
 117. Bice JB, Leechawengwongs E, Montanaro A. Biologic targeted therapy in allergic asthma. *Ann Allergy Asthma Immunol* 2014;112:108-15.
 118. Chung KF. New treatments for severe treatment-resistant asthma: targeting the right patient. *Lancet Respir Med* 2013;1:639-52.
 119. Good JT Jr, Kolakowski CA, Groshong SD, Murphy JR, Martin RJ. Refractory asthma: importance of bronchoscopy to identify phenotypes and direct therapy. *Chest* 2012;141:599-606.