

Biologic and New Therapies in Asthma



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KEYWORDS

• Biologics • Asthma • Anti-IL-5 • Anti-IL-13 • Anti-IL-4 • Th2 • CRTH2 • Anti-IgE

KEY POINTS

- T2-high asthma patients are identified by elevated sputum or blood eosinophils, fractional exhaled nitric oxide (FeNO), and antigen-specific immunoglobulin E (IgE).
- T2-low asthma patients are identified by increased neutrophils or paucigranulocytic findings in the sputum.
- T2-low asthma patients respond poorly to corticosteroids and new biologics approved for asthma.
- T2 targeted therapies discussed in this review include antagonists of interleukin-5 (IL-5), IL-13, IL-4, chemoattractant receptor homologous molecule on T2 cells, and IgE.

INTRODUCTION

Asthma is a complicated chronic disease that affects people from childhood to the elderly. In the United States, approximately 17.7 million adults and 6.3 million children have asthma. In 2011, 1.8 million emergency room (ER) visits carried a primary diagnosis of asthma. The average length of hospitalization for patients with asthma was 3.6 days. In 2013, the average number of lost school days was 13.8 million, and the average number of lost work days was 10.1 million. From 2006 to 2010, approximately 38% of children and 50% of adults with asthma had uncontrolled symptoms. An estimated cost of US\$19.7 billion annually makes asthma 1 of the top 10 prevalent conditions impacting health care system costs.¹ The question remains, why with current therapeutic regimens are patients still uncontrolled? Phenotypic heterogeneity among asthma patients contributes to the variable severity and control of the disease.

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Traditional classification of patients with asthma reflected associated triggers, including exercise, viruses, cigarette smoke, allergens, and aspirin. The National Institutes of Health-sponsored Severe Asthma Research Program (SARP) used cluster analysis to provide unbiased methods to define various asthma phenotypes. The SARP data, as well as other studies, indicated that early-onset disease is consistently associated with more atopy and allergic conditions over a range of severities, whereas adult-onset disease is often associated with obesity and was more common in women. A cluster of adult-onset patients with mild airflow obstruction has fewer exacerbations, but another cluster with moderate airflow obstruction is more exacerbation prone.

In categorizing patients by the observable clinical characteristics, researchers are attempting to link these to underlying molecular mechanisms of their disease, in other words, the endotype (Fig. 1). To date, primarily 2 endotypes of asthma are described, Th2-high (T2 high) and Th2-low (T2 low).^{2–4} Patients with Th2-high asthma have increased eosinophils in their sputum and airways, whereas T2-low asthma patients have either an increase in neutrophils or a paucigranulocytic (minimal inflammatory cells) profile in their sputum and airways. In this review, the focus is on defining what is currently known about the pathophysiology of underlying inflammation intrinsic to these endotypes, including key pathways and cytokines, to better target therapy. Furthermore, the utility of point-of-care biomarkers to guide optimal treatments with controllers and especially biologics is discussed. This step is the first step in precision medicine where medications are targeted toward patients with the anticipation of optimal therapeutic effect.

PATHOPHYSIOLOGY

T2-Low Asthma or Non-T2 Asthma

Studies of patients with severe asthma unresponsive to typical therapeutic regimens in the 1990s illustrated that some of these individuals had neutrophilic inflammation.⁵ Only about 50% of patients with severe asthma exhibit increased eosinophils along with heightened expression of transforming growth factor β and increased synthesis of collagen beneath the bronchial subepithelial basement membrane.⁵ The subset of patients with neutrophil predominance does not exhibit typical T2 cytokines. Neutrophil-predominant patients typically have an onset of disease in adulthood and are generally less corticosteroid responsive. Key cytokines involved in the pathogenesis of these patients include those produced by T helper 1 (Th1) and Th17 cells. The role of Th17 cells and IL-17 in asthma is not defined; however, in experimental asthma models, IL-17A contributes to airway remodeling by stimulating fibroblast proliferation.^{6,7} IL-17 is also increased in sputum of patients with severe asthma and can induce the production of IL-8, a potent neutrophil chemoattractant. In a clinical trial targeting IL-17A, IL-17F, and IL-25 via inhibition of the IL-17 receptor α , there was little benefit in patients with mild to moderate asthma.⁸ It is important to note that patients with sputum neutrophilia were not enriched for in this study, and this could have resulted in the overall lack of efficacy. Other targets evaluated for this endotype include antagonists of tumor necrosis factor (TNF)- α and IL-1. These proinflammatory cytokines are upregulated in asthmatics with neutrophilic inflammation.⁹ Blocking TNF- α in severe asthma has had variable success, but a relatively high risk of adverse effects has resulted in a lack of further clinical development for asthma.¹⁰

Interleukin-8 (IL-8) is a potent mediator of neutrophil chemotaxis through the chemokine receptor CXCR2. A CXCR2 antagonist has been studied for potentially treating neutrophilic airway inflammation. In preliminary study of 12 patients with increased

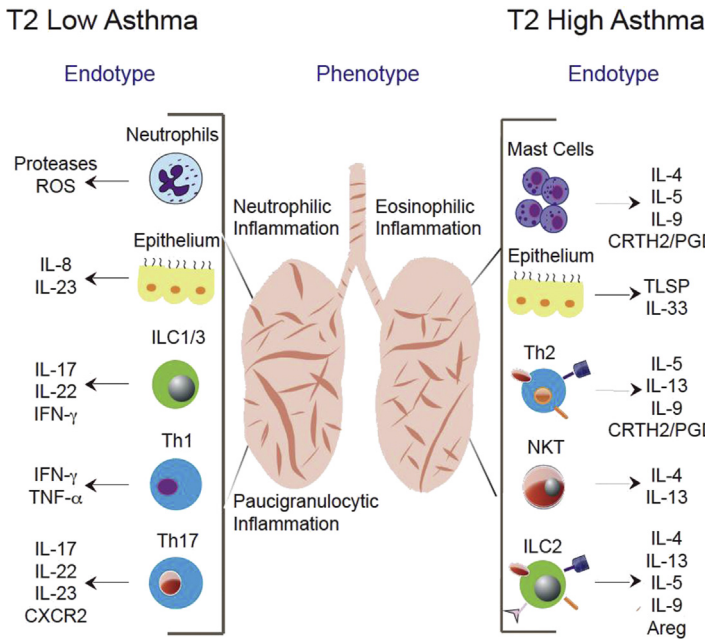


Fig. 1. Different inflammatory patterns in the airways contribute to the underlying inflammation in asthma. In a T2-low pattern, a predominance of neutrophils or paucigranulocytic inflammation has been described. Patients with this phenotype are less likely to respond to corticosteroids. In neutrophilic-predominant disease, patients might respond to antibodies that block $\text{TNF-}\alpha$, IL-17, IL-23. Innate lymphoid cells group 1 and group 3 are more predominant in Th2-low disease. These cells produce IFN- γ , IL-17, and IL-22. A T2-high inflammation is suggestive of eosinophilic phenotypes and is more likely to respond to corticosteroids. A multitude of inflammatory cells and cytokines is involved, but targeting specific type 2 cytokines has proven to be an effective strategy, including antagonists of IgE, IL-5, IL-13, and CRTH2. IFN- γ , interferon gamma; ILC1, type 1 innate lymphoid cells; ILC2, group 2 innate lymphoid cells; ILC3, group 3 innate lymphoid cells; NKT, natural killer cells; PGD₂, prostaglandin D₂; ROS, reactive oxygen species. (Adapted from Muraro A, Lemanske RF, Helings PW, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy, Asthma & Immunology. *J Allergy Clin Immunol* 2016;137(5):1347–58; and Sonnenberg GF, Artis D. Innate lymphoid cells in the initiation, regulation and resolution of inflammation. *Nat Med* 2015;21(7):698–708.)

neutrophils in sputum, targeting IL-8 by using a CXCR2 blocker reduced the sputum neutrophils but without statistical improvements in forced expiratory volume in 1 second (FEV1) or symptom-control scores.³ Most attempts at targeting key mediators of neutrophilic inflammation have not proven very effective therapeutically. Furthermore, the lack of reliable biomarkers associated with neutrophilic predominant asthma has contributed to the difficulty of identifying these patients for targeted therapy. In the case of paucigranulocytic inflammation, with normal levels of eosinophils and neutrophils in sputum and the airways, using intensive bronchodilator therapy with long-acting muscarinic receptor antagonists and/or long-acting beta-receptor agonists is of some benefit. These patients also are relatively corticosteroid resistant presumably due to the limited airway inflammation. Alternatively, these patients with paucigranulocytic inflammation may be candidates for bronchial thermoplasty to reduce airflow obstruction.¹¹

T2-High Asthma

Allergic disease is associated with T2-high inflammation. Typically, patients with childhood-onset asthma before the age of 12 have a history of other atopic diseases. The master regulators IL-33, IL-25, and thymic stromal lymphopoietin (TSLP) stimulate the innate or adaptive immune system to secrete cytokines IL-4, IL-5, and IL-13 (T2-high cytokines) (Fig. 2). The accumulation of these type 2 cytokines stimulates key inflammatory cells, such as eosinophils, mast cells, and basophils. In fact, both IL-4 and IL-13, through the activation of the transcription factor GATA3, regulate T2 inflammation. IL-13 and IL-4 are both involved in activation of B-cell isotype switching to produce immunoglobulin E (IgE). IL-5 is central for eosinophilic development, survival, and chemotaxis. Innate lymphoid type 2 cells (ILC2) are also involved in the production of IL-5 and IL-13. Type 2 cytokines also contribute to mucous cell hyperplasia and fibrosis leading to airway remodeling.²

Patients with airway eosinophilia typically respond to corticosteroids. However, the degree of response is variable.^{12,13} The concept of T2-high disease came from a variety of studies, including those by Haldar and colleagues,^{14,15} where they used molecular phenotyping of airway epithelial brushings from corticosteroid-naïve

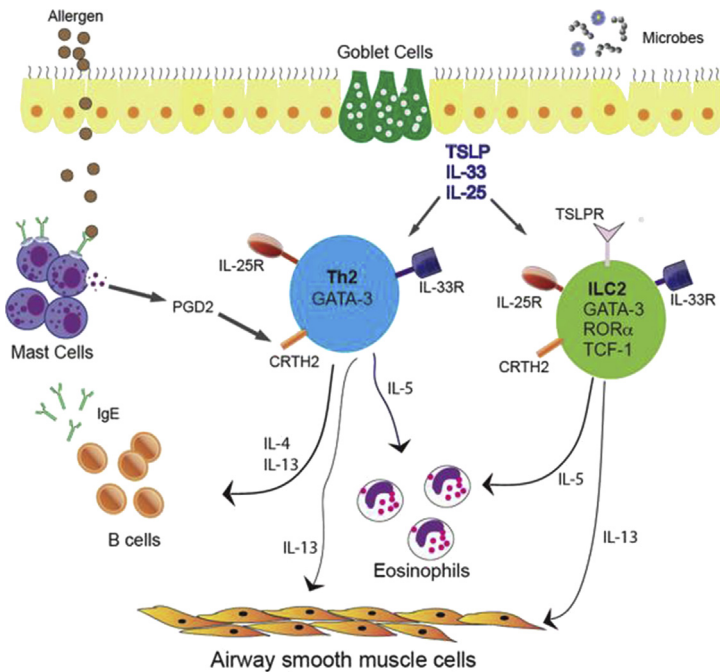


Fig. 2. A very complex interplay of type 2 cytokines and T2-high inflammation. Activation of epithelial cells produces TSLP, IL-25, and IL-33, which stimulates T2 and ILC2s. T2 and ILC2s share many features including the expression of transcription factor GATA-3 and production of type 2 cytokines. Secretion of IL-5 from both of these cells stimulates the production of eosinophils in the bone marrow and elicits the migration of eosinophils to the area of inflammation. IL-5 and IL-13 contribute to smooth muscle changes and remodeling changes. IL-4 contributes to IgE class switching in B cells. GATA-3, transcription factor; RORα, retinoid-related orphan receptor alpha, nuclear receptor; TCF1, T cell factor 1; TSLP, thymic stromal lymphopoietin. (Adapted from Lambrecht BN, Hammad H. The immunology of asthma. *Nat Immunol* 2015;16(1):47.)

asthmatic patients. Subjects defined as having T2-high disease were more apt to have IL-13 and IL-5 messenger RNA, higher number of eosinophils and mast cells, and more atopy compared with T2 low asthma.

T2-related targets that have been examined include IgE, IL-5, IL-13, IL-4, IL-9, IL-4 receptor alpha, chemoattractant receptor homologous molecule on T2 cells (CRTH2), and TLSP.¹⁶ Targeting cytokines and mediators is more successful in appropriately selected patients. In a certain population of patients, clinical benefits have been demonstrated with IgE, IL-5, IL-13, IL-4 receptor alpha, TLSP, and CRTH2 antagonists. The remainder of this review focuses on the discussion of current biologics targeting T2 inflammation and the utility of clinical biomarkers to help guide precision medicine choices (**Table 1**).

Current Biomarkers in T2-High Inflammation

Currently available biomarkers may assist clinicians in the selection of targeted asthma treatments, most of which are specific for T2-high disease. Biomarkers in medicine are divided into 3 categories¹⁷:

- Type 0, a marker that relates to the natural history of disease;
- Type 1, a marker that reflects drug activity or drug responsiveness;
- Type 2, a marker that acts as a surrogate and defines potential disease process.¹⁷

With biologics, defining type 1 biomarkers would facilitate selection of patients with severe asthma that would likely respond therapeutically. Current biomarkers unfortunately are not adequate for identifying early-onset asthma nor are they necessarily accessible to clinicians in the outpatient clinics.⁵ Nonetheless, T2 inflammation may be recognized by an increase in eosinophils in sputum and/or blood. Indeed, both elevated blood and sputum eosinophils are biomarkers for risk of asthma exacerbations. Many studies have shown better responses to biologics with persistent T2 inflammation despite inhaled or systemic corticosteroids. Clinically, it is difficult to measure eosinophils in the sputum,¹⁸ and blood eosinophils levels are variable. Current research suggests that other markers for eosinophils may be useful. Eosinophil granule proteins, such as eosinophil peroxidase (EPX) in sputum, correlate with respiratory disease activity, including asthma and chronic bronchitis in chronic obstructive pulmonary disease. A strong association has been found with nasal and pharyngeal EPX and sputum-induced eosinophils. Currently, a bioactive paper strip is being developed to use as a point-of-care measure in the clinical setting to measure EPX.^{19,20} This quantitative tool could potentially be used as a biomarker to provide better management for poorly controlled patients.

Another marker for T2 inflammation is the concentration of exhaled nitric oxide (fractional exhaled nitric oxide or FeNO). FeNO is a product of the T2-regulated induction of nitric oxide synthase, which generally correlates with eosinophilic inflammation. The American Thoracic and European Respiratory Societies have established parameters for FeNO levels. Normal FeNO is <25 ppb.^{17,21} In a study by Mehta and colleagues,²² in patients with mild to moderate persistent asthma who were treated with mometasone furoate 400 µg/d for 8 weeks, a significant decrease in FeNO was observed as soon as 1 week after the initiation of treatment with Inhaled corticosteroids (ICSs). Patients with high FeNO are more likely to benefit from ICS with change observed as soon as 1 week after the initiation of ICS treatment. If the FeNO values remain at or greater than 50 ppb despite ICS, then corticosteroid resistance or noncompliance should be considered.^{17,21,23,24} Similar to eosinophil counts, FeNO is predictive of asthma exacerbations. In fact, particularly in children a FeNO greater than 49 ppb within 4 weeks of discontinuing therapy with ICS was associated with asthma exacerbations.^{17,25} An

Table 1
Summary of therapies approved or in clinical trials targeting T2-high severe persistent asthma

Current Therapies	Mechanism of Action	Potential Biomarkers	Effect	FDA Approved	Route	References
Omalizumab	Blocks IgE interaction with FcεRI	Elevated IgE. Patients with higher FeNO and blood eosinophils >300 cells/μL better response	Decrease asthma exacerbations	Yes; ages 6 and older	150–375 mg subcutaneous (SC) every 2–4 wk; frequency based on IgE and body weight Black box warning for anaphylaxis	30,32,33
Mepolizumab	IL-5 antagonist	Peripheral eosinophil count of >150 cells/μL or 300 cells/μL	Decrease in asthma exacerbations and improvement in pre-, postbronchodilator FEV1	Yes; ages 12 and older	100 mg SC every 4 wk; consider shingles vaccine before administration	18,26,34–36
Reslizumab	IL-5 antagonist	Peripheral eosinophil count of >400 cells/μL	Decrease in asthma exacerbations and improvement in FEV1	Yes; 18 and older	3 mg/kg IV every 4 wk Black box warning for anaphylaxis	40,42,43
In clinical trials						
Benralizumab	IL-5 receptor α antagonists targeting both eosinophils and basophils	Elevated peripheral blood eosinophil count	Decreased asthma exacerbations and in small study used in ER visit setting administration contributed to a 50% drop in exacerbation over 12 wk	Phase 3; 12 and older	20–100 mg every 4–8 wk	44–46

Lebrikizumab	IL-13 antagonist	Elevated periostin and DDP-4	Decrease in asthma exacerbations with minimal in improvement in FEV1	Termination of clinical program	N/A	27,48
Tralokinumab	IL-13 antagonist	Elevated periostin and DDP-4	Decreased in asthma exacerbations and improvement in FEV1	Phase 2b trials	N/A	49
Dupilumab	Inhibits IL-13 and IL-4 by targeting IL-4 α , a common receptor domain for both cytokines	Peripheral eosinophil count of >300 cells/ μ L or sputum >3% with better response, but improvements in all patients	Decrease in asthma exacerbations and improvement in FEV1	Phase 2b trials	200 mg SC every 2 wk or 300 mg SC every 4 wk; administered at home	50,51

increase in FeNO after discontinuation of long-term omalizumab also predicts exacerbations (Ledford D, Busse W, Trzaskoma B, Omachi TA, Rosén K, Chipps BE, et al. A randomized multicenter study evaluating Xolair persistence of response after long-term therapy. *Journal of Allergy and Clinical Immunology*, In press). Of note, IL-5 antagonists decrease blood eosinophil counts but have little to no effect on the FeNO.²⁶ FeNO is generally not affected specifically by atopic status.¹⁷ Smoking and obesity are associated with lower FeNO. Men typically have a higher FeNO than women.¹⁷ Although many confounding factors can impact the measured FeNO value, it can nevertheless serve as a clinical biomarker to predict response to T2 therapeutics.

Another marker that is also reflective of T2 inflammation is blood periostin. Periostin is produced by lung epithelial cells and fibroblasts in response to IL-13. Periostin gene expression is increased in airways of subjects with asthma.^{21,27} In subjects treated with an IL-13 antagonist, those with higher initial periostin level had a greater improvement in FEV1 than those with lower periostin levels.²⁷ Hence, this biomarker may identify patients that are more responsive to an IL-13 inhibitor.

Finally, IgE is a biomarker associated with allergic sensitization and asthma. However, it is too nonspecific to be a good predictive therapeutic biomarker. Anti-IgE therapeutics decrease asthma exacerbations and blood eosinophils.

In 2016, some of the biomarkers described are predominantly research tools and not widely used in clinical practice. However, blood eosinophils and FeNO are readily available. It is also important to realize that all of the available biomarkers are reflective of T2 inflammation. The remainder of the discussion focuses on choosing the correct biologics for severe asthmatics that have a T2 high phenotype.

SPECIFIC THERAPIES TARGETING T2-HIGH PATHWAYS

Targeting IgE

Asthma is associated with allergic disease, emphasizing the roles of IgE and the T2 pathway. IgE binds with high affinity to IgE receptors on mast cells, and subsequent crosslinking by allergen, mast cells release a variety of mediators and cytokines important in inducing airway inflammation. Several approaches have been taken to target the effects of IgE. Decreasing the production of IgE is a novel approach described by Gauvreau and colleagues.²⁸ Quilizumab, an M1 prime antibody, targeted membrane-expressed IgE-positive cells causing cell death and a decrease in production of IgE. Quilizumab lowered serum IgE levels by about 40% and inhibited both the early and the late allergen-induced asthmatic response. Unfortunately, it did not show clinical efficacy in field trials, halting further development.²⁹

Omalizumab, a recombinant, humanized, monoclonal anti-IgE antibody that blocks the interaction between IgE and the high affinity receptor FcεRI, has been on the market more than a decade.³⁰ Another anti-IgE monoclonal antibody that is currently being studied in severe asthma is ligelizumab, which has 30 to 50 times greater affinity for IgE compared with omalizumab.³¹

Omalizumab has been used for 13 years for asthma, but predictive biomarkers of response were not identified until recently. In a retrospective analysis of the EXTRA study, Hanania and colleagues³² found that omalizumab was more efficacious in patients with higher levels of FeNO, blood eosinophils, or blood periostin. Busse and colleagues³³ confirmed that patients with eosinophil counts greater than 300 cells/ μ L responded better to omalizumab with up to a 60% decrease in asthma exacerbations. These data suggest that in patients with higher blood eosinophil levels, omalizumab's effects on exacerbations are similar to those noted for eosinophil-specific IL-5 antagonists (see later discussion). In 2016, the US Food and Drug Administration (FDA)

approved omalizumab for use in children ages 6 to 11 years with moderate to severe perennial allergic asthma.

IL-5-based Therapy

IL-5 is a key cytokine for eosinophil growth, differentiation, and migration to the airways. To date, 2 monoclonal antibody approaches have been studied in clinical trials to block the effects of IL-5. The first approach is to bind to IL-5 itself, and the second approach is to bind to a component of the IL-5 receptor, the alpha chain. The latter leads to the enhancement of antibody-dependent, cell-mediated cytotoxicity, and apoptosis of eosinophils and basophils. Mepolizumab and reslizumab are 2 humanized monoclonal antibodies that bind to IL-5 and are US FDA approved for patients with severe, eosinophilic asthma. Benralizumab binds to the IL-5 receptor and is still in clinical development.

Mepolizumab

In an initial double-blinded, placebo-controlled study, Flood-Page and colleagues³⁴ evaluated patients with uncontrolled, moderate to severe symptomatic asthma despite ICS treatment. Subjects were given 250 or 750 mg mepolizumab intravenously (IV) monthly for 3 months. Compared with placebo, the rate of exacerbations, lung functions, quality-of-life measures, symptoms, and use of short-acting beta agonist were unaffected. However, the number of blood and sputum eosinophil counts decreased significantly in the mepolizumab-treated groups. Subsequent studies targeted patients greater than 12 years of age with elevated eosinophil counts on high-dose ICS with a second controller, with or without the use of oral corticosteroids, and a history of severe asthma exacerbations. Two small proof-of-concept studies illustrated that treatment with mepolizumab reduced the risk of asthma exacerbations.²⁶ Pavord and colleagues¹⁸ in a multicenter, double-blinded, placebo-controlled trial encompassing 81 centers and 13 countries enrolled 621 asthma patients with evidence of eosinophilic asthma. Patients were randomly assigned to placebo or mepolizumab 75 mg, 250 mg, or 750 mg IV every 4 weeks for a total of 13 infusions. The number of clinically significant exacerbations was decreased from 39% to 52% in the treatment groups at all doses. Efficiency of drug was associated with 2 variables: blood eosinophil count and number of exacerbation the previous year. A 2013 meta-analysis of 7 randomized placebo-controlled trials of 1131 patients with eosinophilic asthma treated with mepolizumab showed an improvement in quality-of-life scores and decrease in asthma exacerbations. Lung function was not improved compared with placebo.³⁵

In 2014, a randomized, double-blinded study of subjects with recurrent asthma exacerbations and eosinophilic inflammation compared mepolizumab 75 mg IV or 100 mg subcutaneously with placebo administered every 4 weeks for 32 weeks. Study entry required an eosinophil count of 150 cells/ μ L at screening or greater than 300 cells/ μ L in the previous year. Both active treatment groups experienced a greater than 50% reduction in asthma exacerbations, approximately 100 mL FEV1 improvement, and better asthma quality-of-life scores compared with placebo.³⁶ ER visits and hospitalizations were reduced significantly in both mepolizumab groups as well. A predetermined subanalysis of 177 patients with blood eosinophil counts greater than 500 cells/ μ L treated with 100 mg of mepolizumab subcutaneously showed an 80% reduction in asthma exacerbation and improvement in FEV1 before and after bronchodilator of 132 mL and 222 mL, respectively.

A few studies have investigated the corticosteroid-sparing effect of mepolizumab in subjects with corticosteroid-dependent, eosinophilic asthma. In a small study of 20

subjects on oral corticosteroids for asthma, the addition of 750 mg of IV mepolizumab for 5 months resulted in a reduction of prednisone use by 84% in the active treatment group compared with 48% in patients receiving placebo. Patients in the active treatment group had improvement in lung function and reduction in blood/sputum eosinophil counts up to 8 weeks after the discontinuation of mepolizumab.³⁷ In a larger study of the corticosteroid-sparing effect of mepolizumab, 135 subjects with severe eosinophilic asthma were treated with 100 mg mepolizumab every 4 weeks for 20 weeks. Mepolizumab resulted in a reduction of corticosteroid use by 50% and also decreased asthma exacerbations and improved symptoms.³⁸

Mepolizumab is approved in the United States as add-on maintenance therapy in patients, 12 years and older, with severe asthma of the eosinophilic phenotype. Better responses occur in patients with higher peripheral blood eosinophil counts, but the specific asthma eosinophilic phenotype is not defined in the package insert. Of note, mepolizumab-treated subjects do have an increase in the incidence of *Herpes zoster* outbreaks. Hence, physicians should consider discussion with patients and possibly vaccinate before initiation of treatment. Similar to many of the other biologics, the optimal duration of therapy is undefined, and there is no evidence of treatment-induced asthma remissions. Haldar and colleagues³⁹ reported that after the cessation of mepolizumab, symptoms recur and serum eosinophil levels increase to the pre-treatment levels. Mepolizumab is not currently approved for any other eosinophilic conditions nor is it indicated for acute bronchospasm or status asthmaticus.

Reslizumab

Reslizumab is also a humanized anti-IL-5 monoclonal antibody. This biologic was FDA approved in 2016 for add-on therapy for severe eosinophilic asthma. Initial studies with IV reslizumab 3 mg/kg in poorly controlled, severe asthma patients, unselected for higher blood eosinophils, did not show much clinical benefit. Subjects treated for 16 weeks did have a decrease in sputum and peripheral blood eosinophil counts.^{40,42} Castro and colleagues⁴³ reported 2 simultaneous double-blinded, multi-center studies enrolling patients between the ages of 12 and 75 years with eosinophil counts greater 400 cells/ μ L. Subjects were randomized to IV reslizumab 3 mg/kg or placebo. The primary endpoint was asthma exacerbations. Enrollment requirements were specified as poorly controlled disease requiring greater than medium-dose ICS plus another controller therapy and with reversibility to short-acting beta-agonist. Study candidates also had at least one asthma exacerbation in the prior year and a blood eosinophil count of 400 cell/ μ L or greater. The active treatment group demonstrated a significant decrease in asthma exacerbations (relative risk = 0.4–0.5) and a significant improvement in FEV1. Bjermer and colleagues⁴¹ and Corren and colleagues⁴² (*Chest*, 2016, in press) showed in a similar patient population significant improvements in lung function, asthma control, and quality-of-life measures. Reslizumab is administered at 3.0 mg/kg IV over 20 to 50 minutes. There is a black box warning for a small (<0.3%) risk of anaphylaxis.

Benralizumab

Benralizumab targets the IL-5 receptor α on eosinophils and basophils and results in apoptosis of these key cells. Similar to the other IL-5 inhibitors, it does result in decreases in sputum and peripheral blood eosinophils.⁴⁴ Castro and colleagues⁴⁵ in a phase 2b trial in uncontrolled, eosinophilic asthmatics studied the impact of variable doses of benralizumab compared with placebo.⁴⁶ Benralizumab was administered every 4 weeks for the first 3 doses and subsequently every 8 weeks for 1 year. A decrease in exacerbations occurred in the 20-mg and 100-mg doses. In the same study, a 1:1 ratio comparison

of placebo and 100 mg of benralizumab was examined in a noneosinophilic population. The subjects in the noneosinophilic population did not show benefit in comparison to placebo or those subjects with eosinophils greater than 300 cells/ μ L, who had an improved FEV1 of 200 mL. Subsequently, Nowak and colleagues⁴⁶ showed that asthma exacerbations over 12 weeks were decreased by 50% in patients treated with one dose of benralizumab during an acute asthma flare requiring an ER visit.

IL-13-based Therapy

IL-13 has many roles in T2 inflammation, including IgE synthesis, proliferation of bronchial fibroblasts, induction of airway hyperresponsiveness, enhanced mucus production, and recruitment of eosinophils and basophils.⁴⁷ IL-13 stimulates bronchial epithelial cells to produce dipeptidyl peptidase-4 (DPP-4) and periostin. Both periostin and DPP-4 are molecules used as biomarkers to predict response to IL-13 antagonists. Corren and colleagues²⁷ in 2011 conducted a randomized double-blinded, placebo-controlled study with lebrikizumab, an IL-13 antagonist, in 219 adults with inadequately controlled asthma despite ICS. Patients were treated with 250 mg of subcutaneous lebrikizumab or placebo for 6 months. Subjects receiving lebrikizumab had a 5.5% improvement in FEV1 compared with placebo. Those treated with lebrikizumab who had a higher periostin level had 8.2% improvement in FEV1 compared with 1.6% in subjects with low periostin levels. Subjects with FeNO who were treated with lebrikizumab had a greater improvement in FEV1 as well. However, no improvement was noted in asthma symptoms scores or exacerbations.

In contrast, a phase 2 study looking at the effect of subcutaneous lebrikizumab at 125, 250, and 500 mg monthly in asthmatics not receiving ICS demonstrated no significant improvements in FEV1, peak expiratory flow (PEF), asthma control questionnaire (ACQ) scores or the frequency of albuterol use.

Hanania and colleagues⁴⁸ showed that patients with severe asthma who had levels of periostin ≥ 50 ng/mL had a reduction of 80% in asthma exacerbations when treated monthly with 125 or 250 mg of lebrikizumab subcutaneously. These patients also had statistically and clinically meaningful increases in FEV1. On the other hand, patients treated with lebrikizumab who had low periostin did not show improvement in FEV1. Duplicate phase 3 trials have illustrated variable results, with one study showing positive results and the other not, even if enriched with patients having elevated periostin levels. These phase 3 study outcomes resulted in the termination of the asthma program for this agent.

Another IL-13 antagonist, tralokinumab, in phase 2 trials at 150, 300, or 600 mg dosed biweekly for 12 weeks with subsequent 12-week follow-up, failed to demonstrate improvement in asthma symptoms scores. Brightling and colleagues⁴⁹ showed treatment with tralokinumab biweekly for 52 weeks did not improve asthma exacerbation rates compared with placebo. However, subjects with elevated periostin or DDP-4 levels or greater airway reversibility did have significantly lower exacerbations and better improvements in FEV1.

Dupilumab is a fully humanized monoclonal antibody that inhibits IL-13 and IL-4. This biologic targets the IL-4 α receptor, which is a common receptor domain for both of these cytokines. In patients with moderate to severe asthma on ICS plus an LABA with elevated peripheral blood eosinophil counts ≥ 300 cells/ μ L or greater than 3% sputum eosinophils, dupilumab reduced asthma exacerbations compared with placebo. Wenzel and colleagues⁵⁰ demonstrated a primary outcome of 87% reduction in asthma exacerbations in patients treated weekly subcutaneously with dupilumab primarily administered at home. Wenzel and colleagues⁵¹ recently showed a biweekly dose of dupilumab administered at home results in improvements in

asthma exacerbations and pulmonary function regardless of pretreatment blood eosinophil levels. However, the data were better for patients having a blood eosinophil level greater than 300 cells/ μ L. Dupilumab is currently being studied in other disease states, including nasal polyposis and atopic dermatitis. It is anticipated that it will be approved for the later disease processes before it achieves an indication for asthma.

Prostaglandin Antagonists

Chemoattractant receptor homologous molecule on T2 cells (CRTH2) is expressed on T2 lymphocytes, ILC2s, eosinophils, and basophils. Prostaglandin D2, which is predominantly secreted by mast cells, binds to CRTH2 and subsequently promotes secretion of IL-5 and IL-13 from ILC2 and Th2 cells, contributing to local airway inflammation.⁵² Initial studies with CRTH2 receptor antagonists show variable results. However, CRTH2 receptor antagonists improve FEV1 in patients with blood eosinophil counts greater than 250 cells/ μ L. Further studies enriching for patients with higher blood eosinophil levels should be considered.

SUMMARY

In summary, all of the biologics currently FDA approved for asthma target T2-high patients. Unfortunately, 50% of patients with severe asthma do not fit this phenotype of disease. Clinicians have access to biomarkers such as total IgE, FeNO, and peripheral blood eosinophils to more appropriately use the current biologics on the market. However, precise biomarkers to predict better responses to specific T2-high asthma therapies are lacking. For example, elevated blood eosinophils track with better responses to all of the T2-targeted therapies and do not allow us to discriminate whether a patient is more likely to respond to one or another. It is important to note that none of the current medications targeting the T2 pathway induce persistent immunomodulation or remission. Once stopped, patient's symptoms and disease manifestations reappear, which is suggestive that the underlying disease process has not been modified. Overall, practicing precision medicine will help decrease associated costs and the burden of disease by using these medications in the most appropriate patients.

DISCLOSURE STATEMENT

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