



Annual Review of Medicine

New Therapies for Emerging Endotypes of Asthma

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Annu. Rev. Med. 2020. 71:25.1–25.14

The *Annual Review of Medicine* is online at
med.annualreviews.org

<https://doi.org/10.1146/annurev-med-041818-020630>

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Keywords

asthma, phenotype, endotypes, airway inflammation, biologics, clustering analysis, sputum, transcriptomics, T2 inflammation, airway remodeling

Abstract

The presentation, pathobiology, and prognosis of asthma are highly heterogeneous and challenging for clinicians to diagnose and treat. In addition to the adaptive immune response that underlies allergic inflammation, innate immune mechanisms are increasingly recognized to be critical mediators of the eosinophilic airway inflammation present in most patients with asthma. Efforts to classify patients by severity and immune response have identified a number of different clinical and immune phenotypes, indicating that the innate and adaptive immune responses are differentially active among patients with the disease. Advances in the detection of these subgroups using clinical characteristics and biomarkers have led to the successful development of targeted biologics. This has moved us to a more personalized approach to managing asthma. Here we review the emerging endotypes of asthma and the biologics that have been developed to treat them.



INTRODUCTION

Asthma is a chronic inflammatory disease of the airways that afflicts ~7% of the US population (1, 2). In most individuals, it is easily controlled with inhaled corticosteroids (ICS) and bronchodilators, usually combined in a single inhaler. However, many asthmatics do not respond adequately to these therapies and have persistent symptoms and/or exacerbations that require systemic steroids and/or hospitalization. It is estimated that approximately 5–10% of all asthmatics have this refractory form of the disease, now termed severe uncontrolled asthma (see sidebar titled European Respiratory and American Thoracic Society's Definitions of Severe and Uncontrolled Asthma) (3–5). Collectively, these patients cost six- to sevenfold more to treat compared to milder asthmatics and are responsible for over 40% of asthma-related expenditures in the United States (6). Although differences in environmental exposures and medication compliance are important factors that can contribute to this morbid form of the disease, it has become increasingly clear that in many patients the cause is dysregulation of biologic pathways that drive inflammatory and remodeling responses in the airway—dysregulation that does not respond to standard treatments (7).

This concept supports the growing belief that there are multiple pathobiologic subtypes of asthma that are characterized by different types of airway inflammation, degrees of airflow limitation, respiratory symptoms, and severity of disease (8). Each subtype is driven by multiple biologic networks that overlap to varying degrees with other disease subtypes, but cause similar inflammatory, physiologic, and clinical features in most patients (9). Research efforts in asthma are now focused on defining these subtypes using machine learning algorithms, as well as biomarkers that range from traditional clinical features of disease to single blood biomarkers to transcriptomic signatures in the blood and sputum (10–12). There are considerable differences among the subtypes of asthma identified in these studies and questions about the value of each analysis' subtypes of disease. None of these subtyping constructs have proven to be helpful to clinicians caring for patients or to scientists studying the pathogenesis of disease.

EUROPEAN RESPIRATORY AND AMERICAN THORACIC SOCIETY'S DEFINITIONS OF SEVERE AND UNCONTROLLED ASTHMA (3–5)

Severe asthma is asthma that has required treatment with guidelines-suggested medications for Global Initiative for Asthma step 4–5 asthma (high-dose inhaled corticosteroids and long-acting beta antagonists or leukotriene modifier/theophylline) for the previous year, or systemic corticosteroids for $\geq 50\%$ of the previous year, to prevent it from becoming “uncontrolled”; or asthma that remains “uncontrolled” despite this therapy.

Uncontrolled asthma is characterized by at least one of the following features:

1. Poor symptom control: Asthma Control Questionnaire consistently ≥ 1.5 , Asthma Control Test < 20 (or “not well controlled”).
2. Frequent severe exacerbations: flares requiring two or more treatment courses with systemic corticosteroids (≥ 3 days each) in the previous year.
3. Severe exacerbations: at least one hospitalization, intensive care unit stay, or use of mechanical ventilation in the previous year.
4. Airflow limitation: after appropriate bronchodilator withhold FEV1 $< 80\%$ predicted (in the face of reduced FEV1/FVC defined as less than the lower limit of normal).
5. Control dependent on high-dose medication: asthma worsens on tapering of high doses of inhaled or systemic corticosteroids (or additional biologics).

In contrast to this exploratory approach, successful pivotal trial programs evaluating several novel targeted therapies that employed biomarker enrichment strategies have identified phenotypes/endotypes of disease that are more likely to respond to a given drug. This has resulted in a shift in how patients are evaluated in the clinic, looking beyond the physiologic characterization of pulmonary function to defining the biologic expression of disease in each patient so that therapies can be more precisely selected. This is especially relevant in the case of severe uncontrolled asthma, where the selection of an expensive injectable therapy should be as accurate as possible. In parallel to this paradigm shift in the approach to treatment are substantial advances in our understanding of the pathogenesis and biologic networks that underlie the heterogeneity of asthma. Ultimately, what is emerging is a move toward the identification of endotypes, beyond a one-drug-fits-all approach to managing asthma, to a more precise approach that will choose the right drug for the right patient at the right time. Here we review the therapies emerging to treat these endotypes, focusing on the current target population for emerging therapies: patients with severe uncontrolled asthma (13, 14).

EVOLVING IMMUNOLOGY OF ASTHMA

For decades, the classic paradigm of asthma pathogenesis proposed that the adaptive immune response drives chronic allergic inflammation of the airway attributable in part to the activation of CD4⁺ T helper (Th2) lymphocyte populations, an increase in Th2/Th1 cell ratio, and exaggerated expression of Th2-associated cytokines including interleukin (IL)-4, -5, and -13 (**Figure 1**) (15). IL-4 drives naïve B cells to become memory B cells and class switching from IgG to IgE production against inciting antigens. IL-5 drives the proliferation and migration of eosinophils from the bone marrow into the circulation and airway wall and IL-13 activates inflammatory cells and drives mucus production and bronchoconstriction. Human and animal studies in transgenic mice that overexpress IL-13 in the bronchial epithelium have corroborated the potency of IL-13 to mediate many of these pathophysiologic abnormalities (16, 17). Most asthma patients have this type of inflammatory response, which is an accepted endotype of disease and can be identified in the clinic by a positive allergy test (blood-based measurement of allergen-specific IgE or skin testing).

In addition to the allergic inflammatory paradigm, advances toward understanding the innate immune system over the last decade have identified a number of mechanisms, cell populations, and cytokines that have altered the original Th1/Th2 asthma construct. These mediators help explain the presence of several subtypes of asthma commonly seen in clinical practice. The list of cell populations is growing, but in relation to asthma, CD4⁺ Th17 cells, dendritic cells, innate lymphoid cells (ILCs) 1 and 2, and bronchial epithelial cells (BECs) have received the most attention (**Figure 1**). Cytokines or their receptors are the targets of most of the emerging therapeutics, including the alarmins IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), which are produced by bronchial epithelial cells in response to inflammation or injury (independent of the adaptive immune response). These cytokines drive downstream activation of ILC2, yielding large amounts of IL-5 and IL-13, but little IL-4 and no specific IgE production (15). This is clinically relevant for three important reasons. First, it may explain in part why up to 50% of patients with severe asthma lack evidence of a Th2 response (absent specific IgE tests), but have persistent eosinophilic inflammation (18–20). Second, eosinophils (in particular blood eosinophils) and fractional excretion of nitric oxide (FeNO) have emerged as key biomarkers to differentiate asthma endotypes and are now a standard part of the workup of patients with severe asthma. Third, emerging therapies against these mediators of the innate response are likely to be approved by the US Food and Drug Administration (FDA) soon that may work equally well in high-T2 and low-T2 disease (21).



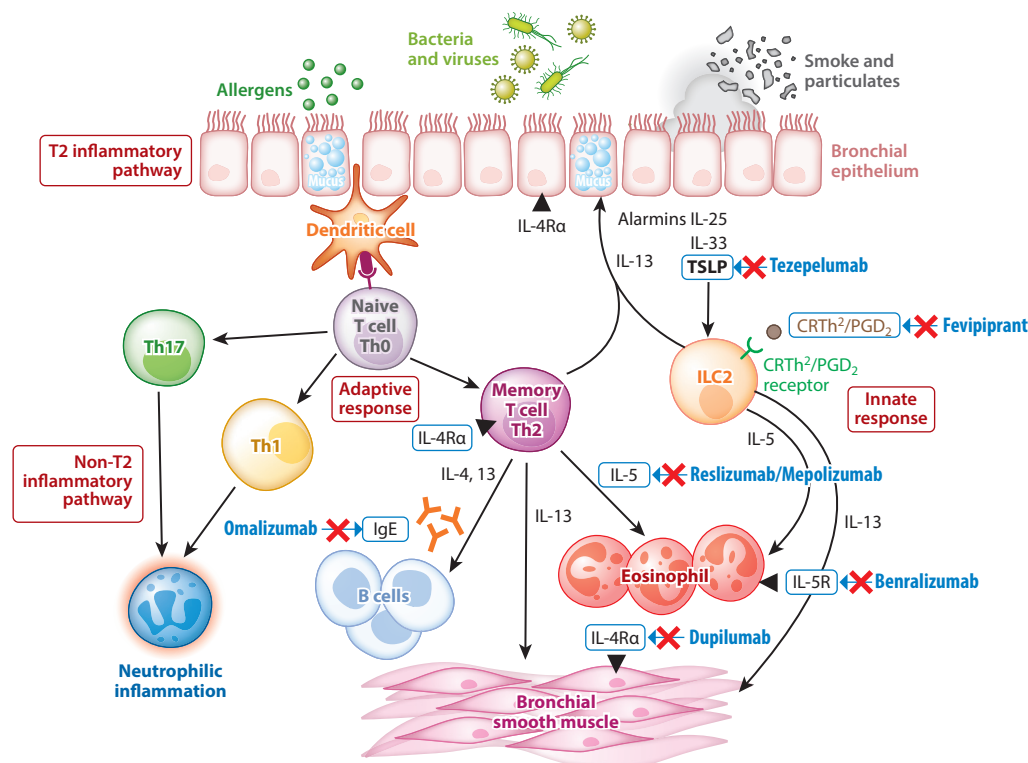


Figure 1

Inflammatory pathways in asthma. The T2 inflammatory pathway with contributions from the adaptive and innate immune response leads to production of T2 cytokines IL-4, IL-5, and IL-13. The non-T2 pathway leads to activation of Th1 and Th17 cells and neutrophilic inflammation. TSLP is the target of tezepelumab; IL-5 is the target of reslizumab and mepolizumab; IgE is the target of omalizumab; CRTh²/PGD² is the target of fevipiprant; IL-4R α is the target of dupilumab; IL5R is the target of benralizumab. Abbreviations: ILC2, innate lymphoid cell 2; TSLP, thymic stromal lymphopoietin.

ADVANCES IN ENDOTYPING PATIENTS WITH ASTHMA

The realization that asthma is an inflammatory disease has led asthma researchers to search for noninvasive biomarkers of inflammation that can aid in the diagnosis, treatment, and monitoring of disease activity. In doing so, the hope is to improve treatment selection for patients with asthma, ultimately moving toward precision medicine. This in turn will improve quality of life; preserve lung function; and reduce healthcare cost, utilization of systemic steroids, and utilization of urgent healthcare resources. Asthma specialists now routinely use the absolute blood eosinophil count, FeNO, and allergy testing (specific blood IgE or skin prick testing) to endotype moderate to severe uncontrolled asthma patients to determine whether bronchial thermoplasty (BT) or a biologic therapy is the best option for the patient.

Although the presence of eosinophils in the sputum in asthma had been noted for decades, only when Green et al. (22) examined the role of sputum eosinophilia in asthma did physicians recognize that adjusting asthma therapy using eosinophil counts could significantly improve outcomes. In this randomized open-label study, subjects were assigned to either standard guideline-driven ICS treatment (the control group) or ICS treatment titrated by sputum eosinophils and symptoms

(the eosinophil-guided group). At the end of the study, the patients in the eosinophil-guided group had significantly lower sputum eosinophil counts and fewer severe asthma exacerbations over the 12-month study period. Subsequently, both sputum and blood eosinophils (above 3% and 300 cells/ μ l, respectively) were used to select patients for treatment with mepolizumab (an anti-IL-5 monoclonal antibody discussed below). This significantly improved the likelihood of reducing severe asthma exacerbations and defined a new subtype of disease: severe eosinophilic asthma (SEA) (23). Blood eosinophils are now a standard test to identify patients with eosinophilic asthma. Blood and sputum eosinophils correlate and are present in both allergic and nonallergic eosinophilic asthma and in disease of all severities, but in the severe uncontrolled asthma patient, blood levels above 150 cells/ μ l are associated with adverse outcomes and an increased likelihood of a response to an anti-T2 biologic therapy (24). The current consensus is that patients with severe uncontrolled asthma and eosinophil counts greater than 150 cells/ μ l have SEA (20, 23). Blood eosinophils are dramatically reduced by systemic steroids and the anti-IL-5 pathway biologics, so they cannot be used to track therapeutic response. In patients with eosinophilic asthma, higher eosinophil counts correlate with features of severity: Those with blood eosinophil counts greater than 300 cells/ μ l were more likely to be taking oral steroids, have fixed airflow obstruction, and have a history of chronic rhinosinusitis and nasal polyposis.

The measurement of FeNO is a noninvasive method to measure airway inflammation. FeNO is a volatile gas produced by the metabolism of arginine, which in the 1990s was shown to be increased in the exhaled breath of asthmatics (25). Other studies have confirmed that FeNO correlates with airway eosinophilia, with a sensitivity of 85–88% and a specificity of 79–90% in diagnosing asthma (26, 27). Inducible nitric oxide synthase expression is induced by IL-13, and FeNO levels positively correlate with levels of airway eosinophils (28). However, despite FeNO's usefulness, poor reimbursement and a lack of prospective trials using it to identify patients for selection of advanced therapies have kept it on the margin of clinical practice in many states. The utility of FeNO for chronic asthma management was evaluated by Smith and colleagues (29), who randomized 97 patients to have their ICS dose adjusted using conventional guidelines or using FeNO measurements. Subjects managed using FeNO measurements required a 40% lower dose of ICS compared to the standard management approach, with no difference in sputum eosinophilia or lung function. The FDA approved FeNO monitoring devices for clinical use in 2003, and FeNO measurement is now a reimbursable test. FeNO levels below 25 parts per billion (ppb) are considered low and T2 inflammation is unlikely, levels of 25–50 ppb are borderline and T2 inflammation is possible, and levels of > 50 ppb are significantly elevated and highly suggestive of T2 inflammation. The 2019 Global Initiative for Asthma (GINA) guidelines suggest that patients inadequately controlled on high doses of ICS are likely to have residual T2 inflammation and be candidates for an anti-T2 biologic therapy (14).

EMERGING THERAPIES FOR SEVERE UNCONTROLLED ASTHMA: BIOLOGICS AND BRONCHIAL THERMOPLASTY

Pharmaceutical companies have successfully developed several agents that target key mediators of the T2/Th2 inflammatory cascades. There are now five monoclonal antibodies clinically available and two or three likely to be approved by the FDA in the next few years for patients with moderate to severe uncontrolled asthma (**Table 1**). The currently available humanized monoclonal antibodies include anti-IgE and anti-cytokine (or anti-cytokine receptor) antibodies that block T2/Th2 inflammation by inhibiting either IgE-mediated allergic responses (anti-IgE, omalizumab) or the biologic effects of T2 cytokines (anti-IL-5, anti-IL-5R, anti-IL-4/13R) on the T2 inflammatory

Table 1 Emerging therapies for severe asthma

Therapy	Mechanism of action	Endotype	Key clinical trial data
Omalizumab	Humanized mAb inhibits activity of IgE	Moderate–severe allergic asthma/IgE ≥ 30 IU/ml, + SPT or specific IgE to perennial allergen	Significantly improved asthma control Decreased exacerbations
Mepolizumab	Humanized mAb inhibits actions of IL-5	Severe eosinophilic asthma/blood eosinophils ≥ 150 or 300 cells/ μ l	Decreased exacerbations by 39–52% Improved quality of life
Reslizumab	Humanized mAb inhibits actions of IL-5	Severe eosinophilic asthma/blood eosinophils $\geq 400/\mu$ l	Decreased exacerbations by 50–59%
Benralizumab	Humanized mAb inhibits actions of IL-5 receptor	Severe eosinophilic asthma/blood eosinophils 300 cells/ μ l	Decreased exacerbations by 45–51% Improved prebronchodilator FEV1 by 0.106–0.159 L
Dupilumab	Humanized mAb inhibits actions of IL-4 and IL-13	Blood eosinophils $\geq 150/\mu$ l FeNO > 25 ppb	Decreased exacerbations by 46–48% Improved prebronchodilator FEV1 by 0.13–0.14 L compared to placebo
Tezepelumab	Humanized mAb inhibits actions of TSLP	Trial criteria: uncontrolled asthma on ICS/LABA; history of exacerbation FEV1: 40–80% pred; post BDR $\geq 12\%$	Decreased exacerbations by 62–71% in phase II trials Reduced blood eosinophils, serum IgE, and FeNO levels
Fevipirant	Small molecule inhibits actions of PGD2	Phase III clinical trial data pending	Improved FEV1 in severe subgroup analysis
Bronchial thermoplasty	Reduces airway smooth muscle mass	Moderate–severe uncontrolled asthma, FEV1 $\geq 60\%$ predicted	Improved composite quality-of-life scores and reduced frequency of severe exacerbations/hospitalizations

Abbreviations: BDR, bronchodilator reversibility; FeNO, fractional excretion of nitric oxide; FEV1, forced expiratory volume in 1 s; ICS, inhaled corticosteroids; LABA, long-acting beta agonists; mAb, monoclonal antibody; SPT, skin prick testing; TSLP, thymic stromal lymphopoietin.

cascade. Targets of therapeutics likely to be approved by the FDA in the near future include anti-alarmin antibodies, anti-TSLP, anti-IL-33R (ST2), anti-IL-25, and a small-molecule oral agent that targets CRTH2 (chemoattractant receptor homologous molecule expressed on TH2 cells).

Omalizumab is a humanized recombinant monoclonal antibody that binds to IgE at the Fc ϵ I receptor binding site, preventing IgE binding to mast cells and basophils. It was the first biologic therapy developed for patients with moderate to severe uncontrolled allergic asthma (defined by an IgE level ≥ 30 IU/ml and sensitivity to at least one aeroallergen) and is dosed using a nomogram that includes weight in kilograms and total serum IgE level. Omalizumab has been shown to reduce exacerbations, rescue albuterol use and dose of ICS, and improve asthma quality-of-life scores in randomized controlled trials (30). In patients with severe persistent asthma still symptomatic on high-dose corticosteroids (fluticasone $\geq 1,000$ μ g per day), omalizumab significantly reduced the amount of ICS needed for symptom control as well as exacerbation rates (31–33). Omalizumab has also been approved for treatment of chronic idiopathic urticaria and for allergic asthma in children aged six years old and older (35, 36).

Several questions have emerged about the use of omalizumab since it entered the clinic over a decade ago. A frequently encountered question is how to adjust the dosage in those patients whose weight (> 150 kg) or IgE level (> 700 IU/ml) is beyond the scale of the nomogram. Most clinicians handle these situations by giving the patients the highest FDA-approved dose of omalizumab if insurance approval can be secured. These patients can respond, which raises the question

of whether the nomogram approach should be changed. Second, there are no known inflammatory biomarkers available to monitor response to or adjust omalizumab treatment, although like all T2 biologics, patients with higher T2 biomarkers (FeNO and blood eosinophil count) are more likely to respond to the drug (33). Lastly, while omalizumab has established a clear position in the treatment of asthma, the addition of four other biologics to the asthma formulary has stimulated interest in determining if there is a right drug for every patient and if some patients will require both anti-IgE therapy to control allergic inflammation and an anti-IL-5-pathway or anti-IL-4/13 therapy to control the T2 inflammatory response. There are no clinical trials examining combinations of biologic therapy, but case reports indicate that this should be an important consideration in some patients (34).

Three anti-IL-5 pathway therapies are currently available for the treatment of severe asthma including mepolizumab, reslizumab, and benralizumab. Pivotal trials for all three drugs have been conducted in patients with severe uncontrolled eosinophilic asthma using slightly different blood eosinophil counts for analysis of the primary endpoints. Wang et al. (37) conducted a meta-analysis to assess the safety and efficacy of all three anti-IL5 therapies including 20 studies with 7,100 patients. Use of anti-IL-5 biologics demonstrated improvement in FEV1 (forced expiratory volume in 1 s), decreased asthma exacerbations, lower levels of sputum and blood eosinophils, and improved quality-of-life questionnaire scores, with no increase in adverse events (37, 38).

Mepolizumab is an IgG1 humanized monoclonal antibody that is directed against IL-5, the canonical growth and activation factor for eosinophils. It is indicated for the treatment of severe uncontrolled eosinophilic asthma (patients whose asthma is uncontrolled on GINA step 4–5 and have two or more systemic-steroid-requiring flares per year) (39). Mepolizumab is delivered in a fixed dose of 100 mg subcutaneously either by syringe or autoinjector. After the first phase III study of mepolizumab failed because there were no biomarker selection criteria, two pilot studies demonstrated that patients with eosinophilic inflammation could respond dramatically to the drug (40–42). In the phase II dose-ranging randomized controlled DREAM trial, patients were enrolled if they had SEA with two exacerbations in the year prior, eosinophils >300 cells/ μ l in the blood or $>2\%$ in the sputum, FeNO ≥ 50 ppb, or prompt deterioration after a 25% decrease in systemic steroid dose at screening (43). Patients treated with three different doses of intravenous mepolizumab had significantly fewer asthma exacerbations than those on placebo. In addition, there was evidence of relapse: 12 months after discontinuing mepolizumab, the number of patients with exacerbations increased, as did their symptom scores. Subsequently, the phase III Mensa study selected patients at lower eosinophil entry criteria of 150 cells/ μ l at screening or 300 cells/ μ l in the year prior and showed that 100 mg delivered subcutaneously reduced exacerbations (39). Mepolizumab was also shown to reduce systemic steroid doses in patients with steroid-dependent asthma and significantly improve disease activity scores measured with the Saint George's Respiratory Questionnaire (41, 44). Long-term efficacy and safety studies show that it is safe to give mepolizumab long-term and that the effect on exacerbations is durable: 53% of patients followed in the open-label study of DREAM had ≤ 1 exacerbation in 4.5 years of follow-up. Mepolizumab has also been approved for the treatment of Churg-Strauss syndrome at a dose of 300 mg subcutaneously per month (45). The most common side effects include nasopharyngitis, upper respiratory infections, and injection site reactions.

Reslizumab, another humanized monoclonal antibody directed against IL-5, is delivered intravenously every four weeks and dosed by body weight (46). Phase III clinical trials showed a decrease in frequency of asthma exacerbations by 50–59% and improvements in FEV1 and quality of life in patients with SEA and blood eosinophils ≥ 400 cells/ μ l at screening (47). A post-hoc analysis looking at late-onset versus early-onset eosinophilic asthmatics showed that reslizumab provided a 75% decrease in asthma exacerbations compared to placebo in late-onset disease compared to



a 42% decrease compared to placebo in patients with early-onset disease (48, 49). Reslizumab's weight-based dosing has been an advantage in obese patients, but the inconvenience and cost of intravenous delivery is hampering its use in practice.

Benralizumab is a humanized IgG4 monoclonal antibody that targets the IL-5 receptor and prevents IL-5 receptor heterodimerization and downstream signal transduction (50, 51). Like mepolizumab and dupilumab, it is approved for SEA that is uncontrolled or systemic-steroid-dependent. It is delivered subcutaneously at a fixed dose every eight weeks after three monthly loading doses. In addition to the inhibitory effect of binding to the IL-5 receptor, the Fc portion of this humanized antibody is afucosylated. This modification increases the affinity for binding of natural killer cells to benralizumab bound to eosinophils and other IL-5 receptor-expressing cells and causes antibody-directed cellular cytotoxicity and apoptosis of the antibody-bound cell. This mechanism of action may explain the potent effect benralizumab has on blood eosinophils and could contribute to its rapid onset of effect (52). This potency has also raised hypothetical concern about the elimination of tissue-resident eosinophils that may have homeostatic or modulatory functions. Since benralizumab targets the IL-5 receptor, it may bypass the effects of increases in IL-5 production that occur during exacerbations. The phase III pivotal trial program consisted of two companion trials, SIROCCO and CALIMA, that examined the effect of benralizumab on exacerbation rates and prebronchodilator FEV1 (53, 54). Although patients were enrolled in the study regardless of their eosinophil count, the a priori primary endpoint was in patients with blood eosinophils ≥ 300 cells/ μ l at screening. Both studies demonstrated that benralizumab significantly reduced annual exacerbation rates (by 51% and 28%, respectively) and improved lung function in the high-eosinophil groups. The ZONDA trial showed that benralizumab reduced systemic steroid dose in oral steroid-dependent patients, and a post hoc analysis showed that onset of effect of this biologic on morning peak expiratory flow was evident within two days of dosing. Benralizumab was safe and well tolerated; headache, pharyngitis, injection site reactions, and hypersensitivity reactions were the side effects reported most commonly in the pivotal trials (55).

The newest biologic to receive FDA approval for the treatment of eosinophilic asthma is dupilumab, an IgG4 κ directed against IL-4R α , which is a coreceptor for both IL-4 and IL-13 pathway signaling (56). This biologic is available in prefilled syringes at two different doses (200 mg and 300 mg) and is delivered subcutaneously every two weeks after a loading dose of two syringes. Dupilumab is the only asthma biologic currently approved for home dosing. It was first approved for the treatment of severe atopic dermatitis, and was approved for the treatment of moderate to severe uncontrolled eosinophilic asthma and steroid-dependent asthma in the fall of 2018 (57). The pivotal trial program examined the effect of dupilumab on steroid-requiring exacerbations, lung function, patient-reported outcomes, and corticosteroid dependence. However, unlike trials examining the efficacy of the other T2 biologics, the phase III dupilumab trials did not analyze patients with higher T2 inflammation for the primary endpoint. Both trials met their primary endpoint and showed that dupilumab decreased exacerbations and improved quality-of-life scores and prebronchodilator FEV1 regardless of the patients' baseline T2 biomarker status. Secondary and post hoc analyses demonstrated that when stratified by eosinophil count or FeNO, the effect of the drug was more predictable in patients with higher T2 biomarkers (i.e., eosinophil count > 150 cells/ μ l or FeNO > 50 ppb). This led to specific labeling for the treatment of eosinophilic asthma. Dupilumab notably reduced total serum IgE levels and FeNO and increased blood eosinophil levels in clinical trials. The side effect profile for patients being treated for asthma is similar to that of other biologics, although patients treated with dupilumab can develop a non-infectious conjunctivitis. This occurred more frequently than in patients on placebo in the atopic dermatitis trials but not in the asthma registry trials. Given the presence of the IL-4 and IL-13

pathway in many atopic diseases, it is not surprising that dupilumab is also effective in chronic sinusitis with nasal polyposis (58). Weinstein et al. (59) examined the effect of dupilumab on perennial allergic rhinitis in patients being treated for concomitant asthma and found improvement in allergic rhinitis symptoms and sino-nasal outcome test scores (SNOT-22).

In addition to the therapies that have recently emerged, several other targeted therapeutics are undergoing clinical trials. Most notable are humanized antibodies directed against epithelial alarmins, such as IL-33 and TSLP, and small molecules against CRTH2. The conventional wisdom is that these targets may lie upstream in the inflammatory cascade, so blockade will affect both the innate and adaptive immune responses and potentially more endotypes of disease, including patients with low levels of T2 inflammation. To this end, the phase II trials of tezepelumab showed improvements in exacerbation rates and reduced blood eosinophil counts, serum IgE levels, and FeNO values (21, 60). Exacerbation rates were lower in patients regardless of the level of T2 inflammation (blood eosinophil counts >140 cells/ μ l and serum IgE levels >100 IU/ml). Tezepelumab has been granted fast-track designation because of the strong phase II results. Phase III studies are ongoing.

CRTH2, also known as PGD2R, is a G protein-coupled prostinoid receptor for prostaglandin D2 that mediates migration and activation of T cells, innate lymphoid cells, and eosinophils. CRTH2 expression is increased in atopic dermatitis, asthma, and allergic rhinitis. An antagonist against CRTH2, fevipiprant, is currently undergoing phase III trials for severe uncontrolled asthma. The phase II study examined patients with mild to moderate uncontrolled allergic asthma (61). Patients were weaned off controller medications and randomized to fevipiprant (500 mg once daily) or placebo for 28 days. Results showed no significant differences between fevipiprant and placebo in FEV1 or asthma control in the intention-to-treat analysis; however, subgroup analyses demonstrated that patients with more severe disease at baseline (FEV1 $<70\%$) had a significant improvement compared with placebo in FEV1 and disease activity, and there were no serious adverse events. The readout for the phase III trial should become available in the fall of 2019.

BRONCHIAL THERMOPLASTY

Hyperreactive, hypertrophied and hyperplastic smooth muscle is a prominent feature of asthma and the target tissue of bronchial thermoplasty (BT), a procedure approved by the FDA in 2014 to treat asthma by structurally altering the airway. It is indicated for patients with severe asthma that remains symptomatic despite adherence to high-dose ICS and long-acting bronchodilators including beta agonists (LABAs) and muscarinic antagonists (LAMAs) (62–70). BT works by reducing airway smooth muscle by delivering radiofrequency energy via a catheter placed through a bronchoscope to airways 3–10 mm in diameter in three treatment sessions. The generation of heat in the airway wall preferentially reduces the mass of the smooth muscle (71). Treatments are at least three weeks apart to different lobes of the lung. Currently the only device approved by the FDA is the Alair® Bronchial Thermoplasty System (Boston Scientific, Marlborough, MA), a single-use system manufactured by Asthmatx, Inc. (Sunnyvale, CA).

The procedure was initially performed in dogs and reported in 2004 (72), followed by a human feasibility trial (73) and a proof-of-concept study (74). The most important efficacy trial of BT was the Asthma Intervention Research 2 (AIR2) Trial, which compared a group of patients receiving BT to a sham procedure group in which subjects underwent bronchoscopy and BT catheter insertion without the application of energy. This trial enrolled 288 severe asthmatics with an FEV1 $\geq 60\%$ and compared the difference in the proportion of subjects whose integrated asthma quality-of-life scores at multiple time points improved by at least 0.5 points for the primary outcome. This endpoint was met in both the intention-to-treat and prespecified per-protocol analyses,

indicating that BT significantly improved quality of life and exacerbations. This study was the only placebo-controlled trial of BT and led to FDA approval of the procedure (75).

The Post-FDA Approval Clinical Trial Evaluating Bronchial Thermoplasty in Severe Persistent Asthma (76) study is a prospective open-label multicenter observational clinical trial assessing the short- and long-term safety and efficacy of BT in a real-world clinical setting. An interim analysis after three years, published in 2017, showed significant decreases in doses of ICS and oral corticosteroids and in rates of severe exacerbations and hospitalizations compared to the year before BT. The side effect profile was similar to that seen in AIR2 (76).

The mechanism of action of BT remains poorly understood. The significant reduction in airway smooth muscle (ASM) after BT has been confirmed by multiple biopsy-based studies (77, 78). One study also showed a significant reduction of nerve fibers in the submucosa and ASM of patients following BT (79), suggesting that BT affects contractile activity of the ASM beyond areas treated.

BT can be considered before regular oral corticosteroid treatment for nonallergic or noninflammatory asthma, or in the case of biologic therapy failure in allergic or eosinophilic asthmatics (80). Patients may prefer BT to biologics because it can be completed in three sessions, in contrast to the burden of taking an injected therapy indefinitely (81). Multiple cost-effectiveness analyses using Markov modeling have shown a high probability that BT is cost effective compared with high-dose combination therapy among severe asthmatics (82, 83) or omalizumab among severe allergic asthmatics (84).

CONCLUSIONS

The progress that has been made in improving our understanding of asthma pathogenesis and treatment has focused on airway inflammation. The variable presence of T2 inflammation in asthmatic populations explains some of the clinical heterogeneity and has led to new approaches to phenotyping asthma. This will undoubtedly lead to a more targeted and cost-effective approach to treatment. The GINA guidelines are embracing the need to address inflammation and are now more intuitive and consistent with asthma specialists' approach to the disease. These guidelines have also integrated the concept of persistent or residual T2 inflammation in patients with uncontrolled disease, so that clinicians have a pathophysiologic construct for what has classically been called steroid resistance. Multiple biologics are now available for these patients, changing the landscape for both patients and clinicians. With these therapies, some patients achieve remission-like control of their asthma, and combination therapy is on the horizon for cases that inadequately respond to treatment with one biologic. Studies should be conducted to identify new biomarkers and algorithms for the next emerging paradigm. It is also likely that the guidelines will need to be re-examined so that expectations for asthma patients can evolve with the therapeutics. For example, the threshold of two exacerbations for prescribing a biologic needs to be reconsidered.

Despite these advances, there are still unmet needs and unanswered questions. There remain no head-to-head trials of emerging biologic therapies or trials comparing biologics to BT, and it is unlikely that any trials will be conducted by industry. This leaves physicians with anecdotal experience, case reports, and retrospective studies for evidence. Patients who have asthma and smoked significantly, who have features of both asthma and chronic obstructive pulmonary disease (COPD), have not been well studied. Recent studies using T2 biologic therapies in this population have failed to consistently reach primary endpoints. This has revealed a need for a more precise approach to identifying patients with COPD that will respond to emerging biologic therapies. Ultimately, as we move forward with dissecting the complex, heterogeneous disease of asthma, it is likely that we will focus on identifying inflammatory endotypes rather than symptoms and physiology for treatment selection.

DISCLOSURE STATEMENT

G. Chupp is on the speakers' bureau/advisory board for AstraZeneca, GlaxoSmithKline, Boehringer Ingelheim, Sanofi, Regeneron, Genentech, and TEVA. R. Kaur and A. Mainardi declare no relevant conflicts of interest.

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