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Review

How to compare the efficacy of biologic agents in asthma

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Key Messages

- Five biologics are approved for treatment of type 2 severe asthma.
- The asthma phenotype for biologics is severe asthma.
- Peripheral blood eosinophils (≥ 150 cells/ μ L) and fractional exhaled nitric oxide (≥ 20 ppb) are biomarkers for T2 inflammation.
- Omalizumab targets immunoglobulin E; mepolizumab, reslizumab, and benralizumab target interleukin (IL)-5-dependent processes; and dupilumab targets IL-4/IL-13.
- The primary outcome improved by T2 biologics is the prevention of asthma exacerbations.
- Mepolizumab, benralizumab, and dupilumab have systemic corticosteroid-sparing actions.

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ABSTRACT

Objective: The use of biologics in severe asthma has made substantial strides in disease management and fostered a personalized medicine approach; however, how, when, and which biologic to choose are unresolved issues, which form the focus of this review.

Data Sources: The data sources were published literature, including current guidelines, available through PubMed searches and online resources.

Study Selection: Studies and randomized controlled trials pertaining to the use of biologics in various phenotypes and/or endotypes of asthma and comparative analyses between biologics in asthma were included.

Results: Inflammatory constructs in asthma are complex and translate differentially into clinical practice for both disease severity and treatment responsiveness. The utilization of biologics, which target selected components of inflammation, has begun to dramatically improve the course of management for many patients with severe asthma. A retuning of our approach into selecting appropriate patient cohorts or phenotypes for studies and selection of clinically relevant outcomes, which are reflected by existing and novel emerging biomarkers, is enabling a paradigm shift in asthma management. Comparing the efficacy of the available biologics for asthma is challenging as no direct head-to-head studies are available, and indirect comparisons to this query provide varying results.

Conclusion: Significant progress has been achieved in the management of severe asthma with treatment of target-specific biologics. Sophisticated algorithms and trial designs, using a combination of available biomarker profiles and clinical characteristics to stratify patient populations into more precise subphenotypes and endotypes to guide our choice of a biologic or therapy, are critically needed but currently not formulated.

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Introduction

Asthma affects approximately 10% of the US population, and worldwide, it is estimated that 300 million people are affected by this disease (www.ginaasthma.org; www.cdc.gov/asthma). One of the emerging and important aspects of asthma is its heterogeneity, which is reflected in many of its characteristics: onset of disease, severity, persistence, and responsiveness to treatment.¹ The subpopulations with severe asthma are of particular importance as they are characterized by incomplete or absent responses to existing treatments resulting in poor disease control and a marker of severe asthma. Collectively, the recognition of asthma heterogeneity, an expanded understanding of the immune-regulated inflammatory pathways in asthma pathophysiology, and the development of biologics that are directed toward specific pathways in the inflammatory response have begun to dramatically and effectively change our approach to a high-risk, high-disease burden population of patients with severe asthma.^{2–6} With new biological agents already approved, the outcomes of these advances have, for many patients, measurably changed their compromised lifestyle and reduced risks for adverse events, such as asthma attacks and adverse effects from the use of systemic corticosteroids. Moreover, the clinical response to intervening with biologics has begun to provide insight into the mechanisms of existing disease in individuals and offers a step toward precision treatment.

Perhaps most importantly, the availability and appropriately guided use of biologics also provide opportunities for improved control of asthma, along with the greater possibility that the selected treatments will offer a greater precision for identifying the inflammatory processes of an individual patient and thus minimize adverse

outcomes associated when a specific inflammatory pathway is unregulated. A major question in the care of severe asthma is, “Is a biologic appropriate for this patient? If so, which biologic should I select? Or, what is the right biologic for the right patient?” Unfortunately, evidence-based answers and precise guidance to these questions are not readily apparent, but data and experience are beginning to provide greater direction in a more learned selection process. Our goal is to provide information and guidance on when to consider a biologic and, if so, which one for which patients.

To meet these goals, our approach will consider the following steps: (1) review the inflammatory mechanisms of severe asthma; (2) discuss current guideline approaches to asthma treatment and potential existing shortcomings; (3) discuss the characteristics of the primary population for whom biologics are being considered—severe asthma; (4) discuss steps that need to be considered before an intervention with a biologic; (5) discuss what biologics are available and what are their effects on asthma outcomes; (6) discuss what comorbid factors may need to be considered in selecting a biologic; and (7) discuss what patient characteristics and biologic comparative evidence are available to guide decision making for selecting an intervention for an individual patient.

Airway Inflammation and Targets for Treatment in Asthma

The characteristics of airway inflammation drive features of asthma but do so with considerable variability.¹ Over the past decade, significant advances have expanded our appreciation of the role of inflammation in asthma, its complexity, heterogeneity, and categorization into type (T) 2 inflammation vs non-T2 inflammation, as well as an arbitrary division of the inflammatory cascade

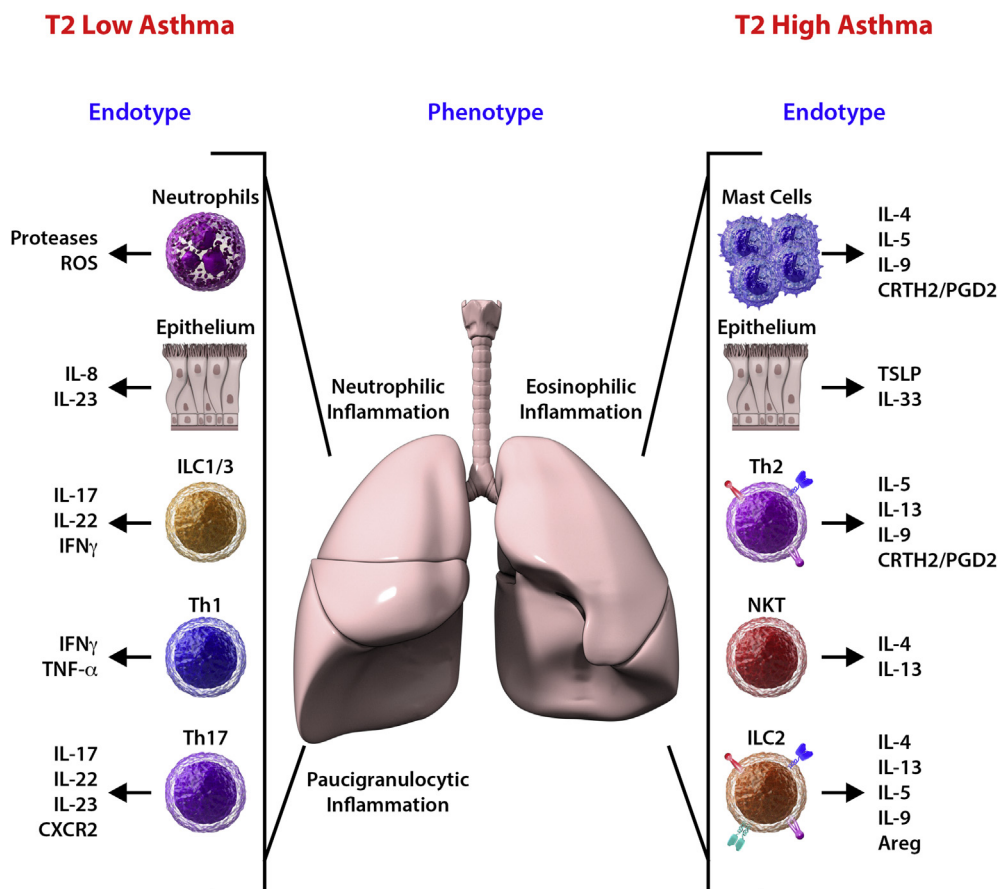


Figure 1. A comparison of the T2-high and T2-low inflammatory response in asthma. CXCR2, C-X-C motif chemokine receptor 2; IFN, interferon; IL, interleukin; ROS, reactive oxygen species; TNF, tumor necrosis factor. Tabatabaian F, Ledford DK, Casale TB. Biologic and new therapies in asthma. *Immunol Allergy Clin North Am*. 2017; 37(2):329–343.

into “upstream” and “downstream” components (Fig 1).⁷ Although these concepts are an oversimplification of the complex and evolving processes that occur in this active and variable disease, they provide a framework to more fully appreciate, understand, and formulate interventions with the new and emerging biologics.

In addition, the recognition of these 2 general pathways has also identified products of inflammation that have begun to not only serve as biomarkers to identify the presence of either T2 high vs T2 low immunity but also direct intervention selections and monitor responses to specific biologic therapy. At present, most biologics available for asthma abrogate the downstream responses, primarily anti-interleukins (IL), that is, IL-4, IL-5, and IL-13. Thymic stromal lymphopoietin is a noteworthy “upstream” master cytokine that is currently being investigated in phase III trials as a target for biologic therapy with tezepelumab for the management of severe asthma.⁸

Initiation of inflammation in asthma begins with activation of the airway epithelium by a variety of “triggers” that include respiratory viruses, allergens, bacteria, and pollutants (Fig 1). This initial stimulus generates a family of alarmins, IL-33, IL-25, IL-6, and thymic stromal lymphopoietin. A subsequent involvement of the T2 inflammatory arm follows with activation of a T_H2 lymphocyte cascade with IL-4, IL-5, and IL-13 generation. Also involved is the innate lymphoid cell (ILC)-2 and its products, IL-5 and IL-13. The inflammatory responses also bring in mast cell, basophil, and eosinophil involvement. Associated with T2 inflammation are products of these processes, which include related biomarkers fractional exhaled nitric oxide (FeNO), eosinophils, and immunoglobulin E (total and antigen-specific IgE). The T2 component of the inflammatory response has been associated with most patients with severe asthma and also serves as the primary target of biologics currently available.

Our knowledge about the non-T2 pathway is both less mature and expansive.⁴ The activated pathways of T1 inflammation include T_H17 and T_H1 cells, with a principal focus on the IL-17 family of cytokines. The airway inflammatory response in non-T2 asthma is primarily characterized by sputum neutrophilia. A recent review by Fitzpatrick et al⁴ provides an overview of the available management strategies for this asthma phenotype. At present, the treatment of non-T2 inflammation remains a major unmet need.

Guideline-Directed Treatment Approaches and Definition and Characterization of Severe Asthma

Guideline-directed treatment for asthma is a step-care approach to disease control. Under this concept, as asthma severity increases, there is a stepwise escalation in the primary treatment medications, inhaled corticosteroid (ICS) in combination with additional controllers, leukotriene modifiers, long-acting β -agonists (LABAs), and/or long-acting antimuscarinic agents (www.ginaasthma.org). Guideline-directed care is largely a “one-size-fits-all” approach; in patients with less severe asthma, achieving disease control has a high likelihood of success. However, a significant and important proportion (5%–15%) of the asthma population does not achieve disease control by this approach and often reaches Global Initiative For Asthma (GINA) step-care 4/5 but continues to remain symptomatic and at risk for exacerbations or systemic corticosteroid use despite efforts to reach control. For patients with asthma at GINA 4/5 treatment level care, modifications in current approaches, including the addition of biologics, are now indicated, and, for many, result in disease control and dramatic changes for future risk and lifestyle. A major impetus to achieving this treatment outcome is to identify eligible patients for the most specific biologic. GINA makes a distinction between difficult-to-treat and severe asthma. In the former group, limited adherence to medication use, poor

inhaler technique and smoking, for example, contribute to poor control. Severe asthma is defined as poor disease control despite optimizing adherence and inhaler technique.

Patients requiring GINA 4/5 level care include difficult-to-treat and severe asthma. Although this group, or phenotype, constitutes only 5% to 15% of all asthma, they experience the greatest disease burden, including risks for exacerbations, increased symptoms, altered lifestyle, a greater degree of airflow obstruction, manifest adverse effects of medications, and utilize health care resources more significantly.⁹ Despite high-dose ICS use, severe asthma also has a greater frequency to need systemic corticosteroids, either as “bursts” or maintenance therapy. The risks associated with even infrequent bursts of corticosteroids have become more appreciated, and avoidance of systemic corticosteroids has become a stated goal of treatment with a more informed use of biologics.^{10,11}

To most accurately and consistently identify patients at greatest risk for poor asthma outcomes and being considered for biologics, the American Thoracic Society and European Respiratory Society proposed a working definition of severe asthma.¹² These consensus characteristics define the high-dose treatment parameters and clinical markers of uncontrolled disease, for example, poor symptom control, frequent severe exacerbation, serious exacerbation/hospitalization or ICU care, and greater airflow limitation. In addition, severe asthma is also defined by those who are controlled but require high-dose ICS, and in some cases systemic corticosteroids, to achieve or maintain disease control.

The GINA Difficult-To-Treat and Severe Asthma Guidelines (www.ginaasthma.org) provide helpful and informed steps to assess patients with asthma at 4/5 care level before beginning biologics. Asthma remains frequently misdiagnosed, which may explain a lack of disease control despite escalation in medication use, and its diagnosis needs to be correctly established.¹³ Other factors that contribute to a lack of disease control include poor adherence to asthma medications, which is a frequent behavior, even with severe disease, and suboptimal technique of use of various inhalers.¹⁴ A diminished response to asthma treatments may be affected by coexisting diseases, such as gastroesophageal reflux, chronic rhinosinusitis with or without nasal polyps, severe allergic rhinitis, vocal cord dysfunction, obstructive sleep apnea, and presence of eosinophilic granulomatosis with polyangiitis (EGPA). Phenotyping for T2 inflammation with basic biomarkers determinations should be made, including measures of peripheral blood eosinophil values (≥ 150 cells/ μ L), FeNO (≥ 20 ppb), and IgE levels along with an identification of allergen-specific sensitization by either skin test or serologic testing. These biomarkers, particularly eosinophils and FeNO, help characterize the inflammatory phenotype: T2 vs non-T2. Some clinical differences between the two are shown in Table 1.⁴

Table 1
Common Features of T2-“High” vs T2-“Low” Asthma

Feature	T2-“high”	T2-“low”
Age of onset	Earlier onset	Later onset
Symptoms	May be significant	May be significant
Life-threatening exacerbations	More exacerbations	Fewer exacerbations
Obesity/metabolic dysfunction	May be present	Often present
Lung function	More obstruction	Less obstruction
Short-acting bronchodilator response	More responsive	Less responsive
Allergic sensitization	Present	Absent
Exhaled nitric oxide	Normal to elevated	Low to normal
Airway eosinophilia	Present	Absent
Airway Neutrophilia	May be present	May be present
Medication requirements	More responsive to corticosteroids	Less responsive to corticosteroids

Table 2
What T2-directed Biologics Are Available for Severe Asthma?

Agent	↓ Exacerbations	↑ Lung function	OCS ↓	Special feature
Omalizumab (IgE)	25%	±	–	Aged >6 y; also approved for CIU
Mepolizumab (IL-5)	50%	+	++	Greatest experience of anti-IL-5s; also approved for EGPA
Reslizumab (IL-5)	50%	++	–	Weight-based dose (intravenously)
Benralizumab (IL-5R)	50%	++	++	Every 8 wk and IL-5R
Dupilumab (IL-4/IL-13)	50%	++	++	Eosinophils, FeNO; also approved for AD and CRSwNP

Abbreviations: AD, atopic dermatitis; CIU, chronic idiopathic urticaria; CRSwNP, chronic rhinosinusitis with nasal polyps; EGPA, eosinophilic granulomatosis with polyangiitis; FeNO, fractional exhaled nitric oxide; IL, interleukin; OCS, oral corticosteroid.

Introduction to the Biologics for Asthma

There are currently 5 T2-directed biologics approved for use in asthma (Table 2) and can be divided into the following 3 general cytokine-targeted pathways: (1) IgE, (2) IL-5 (eosinophils), and (3) IL-4/IL-13 (T2 inflammation). The primary patient population target is defined as having severe asthma with biomarker evidence of T2 inflammation. Goals with the addition of a biologic include the following: (1) reduce exacerbations, (2) decrease need for systemic corticosteroids, (3) reduce asthma symptoms, (4) improve quality of life, and (5) improve pulmonary functions.

In preparation for our discussion on the therapeutic benefits of individual T2 biologics, it is important to appreciate the targeted site of action of the individual biologic (Fig 2).¹⁵

Omalizumab (Anti-immunoglobulin E)

Omalizumab is a humanized anti-IgE monoclonal antibody and was the first approved biologic for the treatment of severe asthma. Omalizumab targets IgE to prevent its binding to its high-affinity

receptor (FcεRI) on mast cells and basophilic leukocytes. The decrease of IgE binding to its receptor reduces expression of the FcεRI on mast cells and basophils with a presumed consequence of decreased mast cell activation by allergens to thereby reduce mast cell-dependent inflammation. Omalizumab is administered subcutaneously every 2 to 4 weeks with a nomogram-based dosing that uses the patient's serum IgE level and weight.

The primary effect of omalizumab has been a reduction in asthma exacerbations, though data indicate that omalizumab may also reduce the need for ICS but not necessarily systemic corticosteroid use. Omalizumab has limited effects on lung function.^{16–18}

Pivotal studies established the efficacy of omalizumab in severe asthma and identified populations of patients most likely to benefit from its use. In 2011, Hanania et al¹⁹ evaluated the efficacy of omalizumab in a large study of patients with severe asthma (850 patients) with more than 1 year of treatment. The enrolled subjects ranged in age from 12 to 75 years, all required high-dose ICS plus a LABA, and a portion of the study population received systemic corticosteroids, prednisone, 2 to 40 mg/d. All subjects had evidence

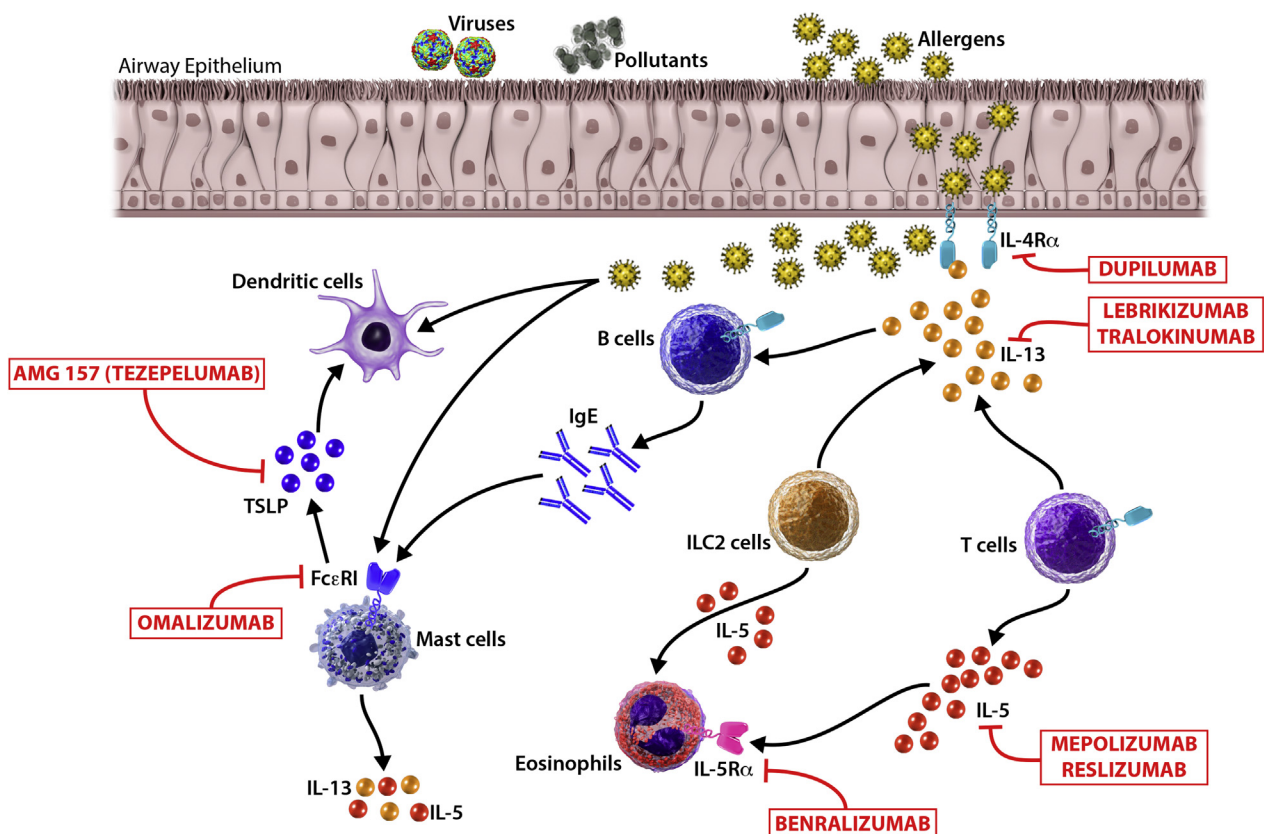


Figure 2. An indication of the sites of airway inflammation that are targeted by current T2 biologics. FcεRI, Fc epsilon receptor; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; TSLP, thymic stromal lymphopoietin.

of IgE sensitization to a perennial allergen (dog, cat, cockroach, or house dust mite) and had forced expiratory volume in 1 second (FEV₁) values of 40% to 80% predicted. The IgE values ranged from 30 to 700 IU/mL. The primary outcome was prevention of an asthma exacerbation, which was significantly reduced by omalizumab vs placebo (incidence rate, 0.66 vs 0.88, $P = .006$), reflecting a 25% reduction in exacerbation rates. Omalizumab had limited effects on exacerbation rates in subjects receiving systemic corticosteroids but improved the quality of life as assessed by the Asthma Quality of Life Questionnaire (AQLQ), reduced mean daily albuterol use, and decreased mean daily symptom scores. No significant improvement in lung function was noted.

A major clinical question has been an identification of the patient phenotype most likely to respond to omalizumab. Although allergic sensitization and IgE values are criteria required for patient selection, the value of the allergen-specific IgE levels or serum IgE concentrations does not consistently predict benefit from treatment with omalizumab. Hanania et al²⁰ had measurements of FeNO (in 46.4% of subjects) and peripheral blood eosinophils (in 93.8% of subjects) in the Exploring the Effects of Omalizumab in Allergic Asthma trial. They found that the FeNO high group (≥ 19.6 ppb) had a greater benefit from omalizumab (53% reduction in exacerbations), whereas no benefit was found in the FeNO low group. Similarly, greater benefit with omalizumab was found in patients in the eosinophil high group, peripheral blood eosinophils greater than or equal to 260 cells/ μ L. Collectively, these data indicate that omalizumab's benefit was primarily found in a T2 high group reflected by elevated FeNO or eosinophil levels.

A proof-of-concept study by Garcia et al¹⁸ found an association between omalizumab's down-regulation of Fc ϵ R1 and improved lung function in patients with refractory nonatopic asthma. These data bolster the observation that the effects of omalizumab extend well beyond the traditional IgE axis. The presence of T2 inflammation and increased FeNO and eosinophils identifies patients for whom omalizumab will most likely benefit. Furthermore, despite omalizumab's primary role to bind IgE, its efficacy in a high eosinophil group suggests that the eosinophil count may have a superior predictive value for response in the hierarchy of biomarkers than the IgE level. Nevertheless, the predictive relationship of eosinophils to omalizumab benefit remains a point of controversy (see subsequent text).

The Inner-City Anti-IgE Therapy for Asthma study was a year-long trial in which omalizumab was evaluated as add-on therapy to guideline-directed care vs guideline-directed care alone. The trial was conducted in children, aged 6 to 17 years, who lived in US urban environments. The addition of omalizumab significantly reduced the frequency of exacerbations, symptoms, and need for ICS. However, greater insight into its effect on asthma exacerbations was seen when analyses compared omalizumab with placebo on a month-by-month basis over the year. Omalizumab's prevention of exacerbation was most dramatic in the spring and, particularly, the fall when children returned to school.²¹ Johnston et al²² had previously analyzed rates and time of the year for annual occurrences of hospitalization for asthma in Canada. Over nearly a 22-year period, rates of hospitalization for asthma spiked in September, shortly after children returned to school. Many factors likely contribute to exacerbations on a return to school in the fall, including outbreaks of viral respiratory tract infections, primarily rhinovirus (RV), late summer and early fall allergic conditions, and under treatment during the summer when asthma is more quiescent. These seasonal yearly flares of asthma are now referred to as the "September epidemic of asthma."

Given the added risk for exacerbations in the fall associated with a return to school, the PROSE study (Preventive Omalizumab or Step-up Therapy for Fall Exacerbations) was designed.²³ The premise of PROSE was to identify school-age children with a history

of asthma exacerbations and then determine whether preschool treatment with omalizumab, limited to a high-risk period of the year, for example, the first 3 months on return to school, would prevent exacerbations. This design was an early step to precision treatment: specific need—prevention of exacerbations at a vulnerable time of the year in an identified high-risk population. In PROSE, an extended run-in phase, 4 to 9 months, was used to stabilize asthma control before treatment randomization.

Omalizumab was initiated 1 month before a return to school and continued for the next 3 months (September through November). A second subject group was given an increase in their ICS dose, but, for safety proposes, did not exceed 1000 μ g/d (fluticasone dipropionate). The third group was on asthma guideline care alone.

A number of significant observations were made in PROSE as follows: (1) There was no significant effect on exacerbation rates with an increase in the ICS; (2) omalizumab significantly reduced exacerbations during the first 3 months of the return to school (odds ratio [OR]: 0.48 [0.25–0.92]); and (3) if an exacerbation had occurred during the 4 to 9 month run-in, the addition of omalizumab had an OR of 0.12, or 88% protection, against exacerbations. In contrast, if no exacerbations occurred during the run-in, there was no effect with omalizumab, primarily because the risk for an exacerbation was small, less than 15%. These findings suggest that benefit from omalizumab could be highly effective when directed with precision to identified risk factors: fall exacerbations and children with exacerbation-prone asthma.

PROSE also provided insight to novel, antiviral effects of omalizumab, based on pilot studies designed to determine if omalizumab affected antiviral activity. Previous work^{24,25} had shown that an in vitro incubation of dendritic cells (DCs) or mononuclear cells with respiratory viruses, including RV, stimulated generation of interferon (IFN)- α , which has antiviral activity. If, however, the DCs or mononuclear cells were from patients with asthma, IFN- α generation to respiratory viruses was diminished and was an IgE-dependent effect. Thus, in PROSE, it was hypothesized that a reduction in cell-surface-bound IgE, which occurs with omalizumab, restores the cellular generation of IFN- α and, possibly, reduces the risk for exacerbations.

To assess this possibility, peripheral blood cells were collected from patients who either received omalizumab or placebo. Peripheral blood cells obtained from patients treated with omalizumab had an enhanced generation of interferon- α to an incubation with RV compared with baseline values. In subjects not treated with omalizumab, interferon generation was unchanged. Moreover, if the restoration of in vitro IFN- α was greater than 50% over the median value, a significant reduction in exacerbations (OR: 0.14) was observed. Although these observations can only infer that omalizumab restores antiviral activity in vivo, additional observations in the PROSE trial²³ point to a decreased susceptibility to RV infections and illnesses during omalizumab treatment.

In constructing the mechanisms associated with omalizumab, its known effects on IgE-mediated mast cell activity suggest benefit arises from reduced mast cell activation and a subsequent diminished inflammatory response. The findings in PROSE suggested that reduced cell-bound IgE also restored antiviral activity by enhancing IFN- α production. Therefore, it is appropriate to consider that the beneficial effects of omalizumab extend beyond its anti-inflammatory activity to include a restoration of antiviral actions. The translation of these concepts to a predictive model of patient selection for omalizumab has yet to be established.

Patient selection for omalizumab is an important clinical question. Although Hanania et al²⁰ found that T2 inflammation biomarkers, for example, FeNO and eosinophils, were associated with the greater likelihood for omalizumab to prevent exacerbations, confirmation of these observations is needed. In the STELLAIR

trial, Humbert et al²⁶ conducted a “real-life” study in France that evaluated medical records of patients treated with omalizumab and used 3 criteria to determine if an effective response occurred: physician evaluation, a reduction of greater than or equal to 40% annual exacerbation rate, and a combination of both. The “responders” were then evaluated in relationship to peripheral blood eosinophil values greater than or equal to 300 cells/ μ L or less than 300 cells/ μ L. In this study of 872 patients with severe asthma, the effectiveness of omalizumab was similar whether eosinophil values were high or low. The question of patient selection for omalizumab based on peripheral blood eosinophils, however, remains unanswered.

Another prospective real-world study, PROSPERO (Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab),²⁷ identified patients aged 12 years and older who were candidates for omalizumab. They were enrolled in a single-arm, 48-week trial. Monthly assessments of clinical characteristics during treatment were made, including exacerbations, health care utilization, asthma control test (ACT), and adverse reactions. In addition, blood eosinophils, FeNO, and spirometry were measured at baseline, 6 months posttreatment, and study completion. Of the 806 subjects recruited, 622 completed the 48-week trial. Exacerbation rates were significantly reduced from 3.0 ± 3.1 , in the preceding years, to 0.78 ± 1.37 at study completion ($P < .001$); ACT scores similarly improved by 4.4 ± 4.9 points, but lung functions were unchanged. An association of the baseline biomarker status (eosinophils) to ACT score and lung function improvement was found, but changes were not clinically relevant. This study, though limited in scope but reflective of clinical practice, did not find peripheral blood eosinophils or FeNO to be predictive markers for omalizumab benefit. More recently, a substudy of the PROXIMO (Patient Reported Outcomes and Xolair In the Management of Asthma) trial indicated a role for using plasma galectin-3 and urine proteomics to stratify responders and predict lung function improvement with use of omalizumab in patients with severe allergic asthma.²⁸ Although intriguing, these results will need to be replicated and validated before being adopted in clinical practice. Overall, at present, there is insufficient or reproducible data to substantiate that T2-specific biomarkers predict the potential for clinical benefit with omalizumab.

Eosinophil-Directed Monoclonal Antibody Treatment of Severe Asthma

Eosinophils are characteristic of airway inflammation in asthma, and peripheral blood eosinophil values predict the risk for asthma exacerbations.²⁹ Similarly, sputum eosinophils ($\geq 2\%$) indicate an increased risk for exacerbation.

The eosinophil biology contributes to characteristic features of asthma and its resulting pathophysiology. Eosinophil granule proteins are toxic to the airway and cause inflammation similar to that seen in clinical asthma. Eosinophils are also a source of cytokines and chemokines, including IL-5, which can further perpetuate ongoing inflammation. Regulation of eosinophil growth and development is largely controlled by IL-5, which directs terminal differentiation, bone marrow release, migration to sites of inflammation, and cell survival. IL-5 activates eosinophils through IL-5R α . The actions and associations of eosinophils with asthma support this cell's potentially important roles in airflow obstruction, risk for and contributions to exacerbations, bronchial hyperresponsiveness, and airway remodeling. Studies with animal models provide highly convincing evidence that blockade of IL-5 ameliorates airway inflammation and airway hyperresponsiveness after allergen challenge. Such observations stimulated considerable enthusiasm and high expectations for dramatic effects in asthma if eosinophils would be reduced by anti-IL-5 treatment.

These optimistic asthma predictions did not materialize in clinical asthma, as repeated trials with various anti-IL-5 monoclonal antibodies failed to reveal efficacy, which was primarily being assessed by an improvement in lung functions. Flood-Page et al,³⁰ however, found a reduction in asthma exacerbations in a small subset of patients who had been treated with an anti-IL-5. These preliminary data suggested that the prevention of exacerbations might be more linked to a role for eosinophils in asthma and be a more appropriate and telling outcome measure to determine efficacy with antieosinophil therapy.

Breakthrough insights on the role and contribution of eosinophils and IL-5 to asthma exacerbations occurred with the findings Haldar et al³¹ at Leicester, United Kingdom. Extending on the findings of Flood-Page et al,³⁰ Haldar et al carefully selected a well-defined patient population for study with the anti-IL-5 monoclonal antibody, mepolizumab. All subjects had severe asthma with a firm diagnosis of asthma (reversibility or airway hyperresponsiveness), a history of at least 2 exacerbations in past year, and sputum eosinophilia ($\geq 3\%$) in the past 2 years. The principal study outcome was the number of severe exacerbations during the year of treatment with mepolizumab. The study was small, 29 on mepolizumab treatment and 32 received placebo. Mepolizumab led to significant reduction in severe exacerbations, defined as a need for systemic corticosteroids, with a relative risk of 0.57 ($P = .02$). There was also an improvement in the quality-of-life measures, but no significant change in FEV₁. Peripheral blood eosinophils were dramatically reduced and sputum eosinophils to a lesser degree. FeNO values, which were increased at baseline, did not change with mepolizumab treatment.

The results of this study with an approximate 50% reduction in exacerbations changed the overall approach to studies with anti-IL-5 therapy by recruiting appropriate phenotypically reflective at-risk subjects—severe asthma with underlying eosinophilia despite ongoing treatment with high-dose ICS, and making the primary outcome an event related to pathobiology of the eosinophil-asthma exacerbations.

Regulation of Interleukin-5 and Asthma Control

Two distinct approaches were developed to regulate IL-5—directed action on eosinophils. Mepolizumab and reslizumab are monoclonal antibodies directed against IL-5 to prevent activation of the IL-5 receptor. Anti-IL-5 therapy dramatically reduces peripheral blood eosinophils and, more variably, airway (eg, sputum) eosinophils.

Benralizumab, in contrast, is a monoclonal antibody directed toward the eosinophil IL-5 receptor and activates an antibody-dependent cellular cytotoxicity response to cause eosinophil apoptosis. Although there is speculation that targeting the IL-5R more effectively reduces eosinophils and leads to greater clinical efficacy, this concept has not been substantiated.

Effects of Anti-interleukin-5 Therapy on Asthma Exacerbations

All 3 anti-IL-5 monoclonal antibodies effectively reduce exacerbations in severe asthma. Mepolizumab was the first to be evaluated for its ability to blunt exacerbations in severe, persistent asthma with eosinophilic inflammation. In the DREAM trial, Pavord et al³² enrolled 621 patients aged 12 to 74 years with recurrent severe asthma exacerbations while on moderate-to-high-dose ICS with other controller medications and signs of eosinophilic inflammation ($\geq 3\%$ sputum eosinophilia or FeNO ≥ 50 ppb or peripheral eosinophil count ≥ 300 cells/ μ L) to receive 1 of 3 doses of mepolizumab or placebo intravenously every 4 weeks for a year. They found a 39% to 52% reduction in the rate of clinically significant exacerbations in patients treated with mepolizumab than with

placebo, whereas other secondary outcomes, that is, FEV₁ and Asthma Control Questionnaire (ACQ)/AQLQ scores, were not significantly affected. In the MENSA trial, Ortega et al³³ evaluated 576 patients with severe asthma with recurrent exacerbations while on high-dose ICS and evidence of eosinophilic airway inflammation; they received intravenously (75 mg) or subcutaneously (100 mg) mepolizumab or placebo every 4 weeks for 32 weeks. They replicated a reduction in the rate of exacerbations by 47% to 53% ($P < .001$) as well as improved FEV₁, ACQ-5, and St. George's Respiratory Questionnaire scores. The results from the MUSCA trial confirmed significant improvements in health-related quality of life outcomes and safety outcomes with the addition of mepolizumab therapy in severe eosinophilic asthma.³⁴ With the mepolizumab trials, efficacy was found in patients with a peripheral blood eosinophil count of 150 cells/ μ L or more, a clear demarcation for patient selection. Moreover, MENSA established the efficacy of subcutaneous dosing of 100 mg per 4 weeks with mepolizumab. Mepolizumab is approved for those aged 6 to 11 years at a dose of 40 mg every 4 weeks. For patients aged 12 years and older, the dose is 100 mg subcutaneously every 4 weeks. At-home administration is available.

Finally, the SIRIUS trial³⁵ enrolled 135 patients with severe, systemic corticosteroid-dependent eosinophilic asthma and demonstrated the ability of mepolizumab to have a significant oral glucocorticoid sparing effect (OR 2.39 higher than placebo, $P = .008$) both in the likelihood of dose reduction and the median percentage reduction from baseline compared with placebo. Significant reductions in exacerbations rates and improvements in ACQ-5 scores were also replicated in this trial.

In 2015, Castro et al³⁶ reported on the results of 2 duplicate phase 3 clinical trials with reslizumab. The subjects enrolled were required to use at least a medium dose of ICS (fluticasone 440 μ g/d), with or without a second controller, have a history of at least 1 asthma exacerbation that required systemic corticosteroids in the past year, have inadequate asthma control (ACQ ≥ 1.5), and a peripheral blood eosinophil count of ≥ 400 cells/ μ L. Enrolled subjects ($n = 489$ in study 1 and $n = 464$ in study 2), received either reslizumab (3.0 mg/kg) or placebo every 4 weeks for 1 year. In both study 1 and study 2, a hazard ratio of 0.575 ($P < .001$) and 0.486 ($P < .001$) was achieved in reducing asthma exacerbations. Protection against exacerbations was similar with subjects on ICS $\pm$ LABA, and paralleled the effect with mepolizumab with an approximate 50% reduction in

exacerbations. Statistically significant improvement in lung function (FEV₁) was also noted with reslizumab compared to placebo in both trials. For selection of patients for reslizumab, 400 or more eosinophils per microliter are necessary. Dosing of reslizumab is weight based and fixed at 3 mg/kg and requires intravenous administration.

Simultaneous publications of studies with benralizumab also indicated efficacy of an anti-IL-5R approach on asthma exacerbations.^{37,38} In the SIROCCO trial, Bleecker et al³⁷ enrolled 1205 subjects, who were randomly assigned to placebo ($n = 407$), benralizumab 30 mg every 4 weeks ($n = 399$) or benralizumab 30 mg every 8 weeks ($n = 398$). All subjects were required to use at least medium to high-dose ICS, have evidence of at least 2 documented asthma exacerbations in the past year, an FEV₁ less than or equal to 80% predicted and inadequate asthma control (ACQ-6 ≥ 1.5). Subjects were randomized to treatment in a 2:1 ratio depending on peripheral blood eosinophil values greater than or equal to 300 cells/ μ L or less than 300 cells/ μ L. The primary outcome was the annual asthma exacerbation ratio vs placebo, with a secondary outcome being a change in prebronchodilator FEV₁ vs baseline. Results were compared in subjects with eosinophil values greater than or equal to 300 cells/ μ L vs less than 300 cells/ μ L.

In CALIMA, FitzGerald et al³⁸ reported on the results of 1306 subjects enrolled with similar entry criteria to SIROCCO and treatment distribution: placebo ($n = 440$), benralizumab 30 mg every 4 weeks ($n = 425$), and benralizumab 30 every 8 weeks ($n = 441$). Primary outcomes for CALIMA were similar to SIROCCO.

The efficacy of benralizumab was similar in SIROCCO and CALIMA (Fig 3), though the reduction in the exacerbation rate was less in CALIMA. The reasons for the differential effects in the 2 studies were not apparent although CALIMA had a larger number of subjects from Eastern Europe residents where exacerbation rates were lower. The differences in exacerbation rates in subjects on placebo with eosinophil values greater than or equal to 300 cells/ μ L in CALIMA (0.93) vs SIROCCO (1.33) may have also contributed to the differential outcomes in these 2 studies. The beneficial effects were greater in subjects with blood eosinophil values greater than or equal to 300 cells/ μ L, a selection criteria for benralizumab treatment that can be administered at home and ultimately dosed every 8 weeks.

The Effect of Anti-interleukin-5 Treatment on Lung Functions

Mepolizumab treatment led to moderate improvement of prebronchodilator FEV₁ values.³³ However, both reslizumab and

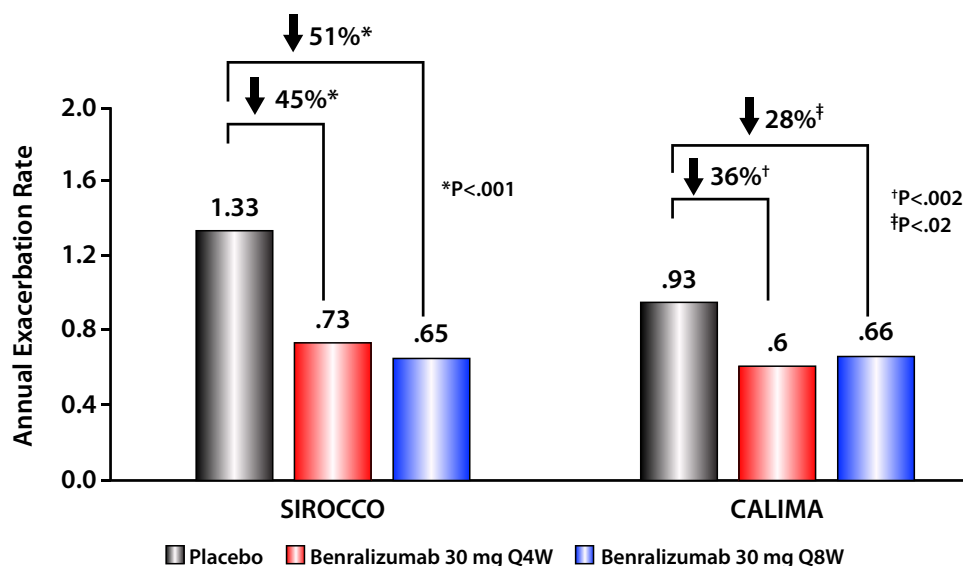


Figure 3. The effects of benralizumab treatment (30 mg every 4 weeks and 30 mg every 28 weeks) vs placebo on the annualized exacerbation rates in SIROCCO and CALIMA trials. Q4W, every 4 weeks; Q8W, every 8 weeks. * $P < .001$; † $P < .002$; ‡ $P < .02$.

benralizumab significantly improved FEV₁ values in subjects enrolled with eosinophil counts greater than or equal to 400 or 300 cells/ μ L, respectively. In SIROCCO, a significant improvement in prebronchodilator FEV₁ (L) values occurred in subjects who received high-dose ICS/LABA and had eosinophils greater than or equal to 300 cells/ μ L when compared with the placebo group. The 30 mg every 4 weeks had a 0.106 L ($P = .02$) improvement in FEV₁, and the 30 mg every 8 weeks led to 0.159 L improvement ($P = .0006$). Improvement in FEV₁ values did not occur in subjects with eosinophil values lesser than 300 cells/ μ L. There was not a consistent effect on symptoms as assessed by ACQ-6.

The mechanisms by which a reduction in eosinophils improves lung function are not established. Many factors contribute to airflow obstruction in asthma, including bronchoconstriction, inflammation, airway edema, airway remodeling (eg, smooth muscle hypertrophy, collagen deposition, and neovascularization), and mucus hypersecretion. Although initial attention on improved lung function has focused on a reduction in eosinophil-generated inflammation, evidence for this effect is not forthcoming despite studies showing reductions in sputum eosinophilia, a surrogate for airway eosinophilic inflammation.

A novel and exciting observation by Dunican et al³⁹ arose when multidetector computed tomography lung scans were used to assess the presence of mucus plugs in the lungs of patients with asthma vs control subjects. The study enrolled 22 normal controls and 146 subjects with asthma, many of whom had been enrolled in the NIH-supported Severe Asthma Research Program and had well-defined severe asthma. The investigators evaluated the relationships between mucus plug scores by lung scans, FEV₁ values and airway eosinophils as measured by sputum analysis. A wider range and higher mucus scores were found in subjects with asthma compared with normal subjects. Subjects with high lung mucus scores also had lower FEV₁ values. The mucus score indices were higher in patients with higher sputum eosinophils and greater concentrations of eosinophilic peroxidase (EPO or EPX), presumably reflecting eosinophil activation. From *in vitro* studies, the investigators demonstrated that activation of blood eosinophils generates EPO, which then converts mucin into mucus plugs. These intriguing findings raise the possibility that reducing airway eosinophils would diminish mucus plug formation, and, with these changes, improve lung function. This concept is intriguing and may be a partial answer for the observed improvement in FEV₁ with anti-IL-5 therapy but needs further assessment, as do other eosinophil-related effects.

Biologics and Regulation of the Interleukin-4/Interleukin-13 Pathway

Generation and overexpression of IL-4 and IL-13 lead to multiple and profound effects on numerous, often interrelated, aspects of airway inflammation and the injury/repair cycle of airway remodeling. Both IL-4 and IL-13 are generated by T_H2 lymphocytes and IL2 cells and can cause B-cell isotype switching to generate IgE, direct eosinophil trafficking from blood vessels to sites of inflammation through up-regulation and generation of chemokines (eg, TARC and eotaxin-3), stimulate epithelial cell mucus production, and affect aspects of airway function including smooth muscle contractility and remodeling.

Dupilumab is a monoclonal antibody directed against the IL-4 α receptor, which is shared by the IL-13 molecule. Consequently, dupilumab has the unique capability of producing a dual blockade of IL-4- and IL-13-dependent pathways. Earlier studies to evaluate strategies to inhibit IL-4 activity found little effect on asthma outcomes. Studies with the anti-IL-13 monoclonal antibody, lebrikizumab, prevented exacerbations and improved airflow obstruction in severe asthma, particularly in a subgroup with

elevated baseline serum periostin, a marker of IL-13 activation. However, failure to confirm these effects in 2 large studies (LAVOLTA 1 and 2)⁴⁰ led to a halt of its development for asthma. Similarly, tralokinumab, another dedicated anti-IL-13 monoclonal antibody, was evaluated for the management for severe uncontrolled asthma through the ATMOSPHERE clinical development program. Unfortunately, reductions in annualized asthma exacerbation rate were not replicated in its pivotal STRATOS 1 and 2 trials,⁴¹ and eosinophilic airway inflammation or oral corticosteroid-sparing effects were not significantly altered in the MESOS trial,^{42,43} halting its development as well.

These observations contrast with dupilumab where more profound benefit is achieved when the pathways of both IL-4 and IL-13 are blocked simultaneously instead of IL-13 alone. Early insight into the scope of dupilumab efficacy in severe asthma was found by Wenzel et al.⁴⁴ Using a unique clinical design in a phase 2A trial, a small number of subjects ($n = 104$) were enrolled. All had ICS/LABA requirements of at least 250 μ g fluticasone/50 μ g salmeterol twice per day, FEV₁ greater than or equal to 50% predicted, a history of at least 1 corticosteroid treated asthma exacerbation in the past 2 years, an ACQ score greater than or equal to 1.5, and a peripheral blood eosinophil count of greater than or equal to 300 cells/ μ L. Subjects were randomized to weekly dosing of dupilumab 300 mg or placebo. After randomization, the 4-week stable therapy phase was followed by a LABA and then ICS treatment reduction. Using this approach to “destabilize” asthma control, the investigators demonstrated efficacy of dupilumab by noting significant improvements in multiple asthma outcomes. The frequency and time to an exacerbation (actually a marker of loss of meaningful asthma control) were improved with dupilumab. The FEV₁ values increased with the addition of dupilumab to ICS/LABA treatment and were sustained with ICS/LABA reductions. Finally, FeNO values fell during treatment with dupilumab. These preliminary findings support broad beneficial effects in asthma with an IL-4/IL-13 blockage by dupilumab.

In 2018, Castro et al⁴⁵ reported on the results of a phase 3 trial, LIBERTY ASTHMA QUEST. Eligibility criteria included the following: a need for high-dose ICS (≥ 500 μ g fluticasone twice a day), plus up to 2 additional controllers, FEV₁ lesser than or equal to 80% predicted, ACQ score greater than or equal to 1.5, and at least 1 exacerbation in the past year. No specific inclusion criteria pertaining to peripheral blood eosinophils or other biomarkers for T2-inflammation were utilized. The primary outcomes were the annualized rate of asthma exacerbations and the absolute change from baseline in the FEV₁ before bronchodilator at 12 weeks of the 52-week trial. Two prespecified dosing regimens were used: 200 mg (400 mg loading dose) and 300 mg (600 mg loading dose) every 2 weeks vs a matched placebo, and a prespecified analysis that included blood eosinophil values of greater than or equal to 300 cells/ μ L vs less. Similar prespecified subgroup analysis were included for FeNO ($>$ or < 25 ppb). Compared with placebo, treatment with dupilumab 200 mg every 2 weeks had relative risk for exacerbations of 0.52, and 0.54 with dupilumab 300 mg every 2 weeks. To gain greater insight and direction toward selecting the patient groups more likely to benefit from dupilumab, the influence of peripheral blood eosinophils and/or FeNO was evaluated in relationship to a prevention of asthma exacerbations. Subjects with peripheral blood eosinophils greater than or equal to 150 cells/ μ L and FeNO greater than or equal to 25 ppb had the greatest protection from exacerbations with dupilumab. In contrast, when peripheral blood eosinophils were lesser than or equal to 150 cells/ μ L and FeNO lesser than or equal to 25 ppb, no significant benefit with dupilumab over placebo was found. When either eosinophils were greater than or equal to 150 cells/ μ L or FeNO greater than or equal to 25 ppb, the benefit of dupilumab over placebo was significant but intermediary to higher values of both eosinophils and FeNO.

These data are a strong indication that a biomarker profile of T2 inflammation, for example, eosinophils greater than or equal to 150 cells/ μ L and/or FeNO greater than or equal to 25 ppb, selects patients with severe asthma more likely to benefit from dupilumab treatment.

Dupilumab, at either 200 or 300 mg/2 weeks, also led to a significant improvement in FEV₁ values from baseline vs placebo. The onset of improvement in the FEV₁ was rapid starting at 2 weeks postdosing and then sustained over the study. Although there was a fall in FeNO values with dupilumab treatment, the relationship of this biomarker change of airway inflammation to improved lung function was not determined.

The Effects of Biologics on Systemic Corticosteroid–dependent Asthma

A more limited set of patients with severe asthma requires maintenance systemic corticosteroids for disease control. It is generally assumed that patients requiring systemic corticosteroids for disease control represent the most severe phenotype of asthma, as their inflammatory pathways are not fully responsive to inhaled corticosteroids and, in addition, are at greatest risk for treatment adverse side effects. Corticosteroids have life-saving actions in severe asthma attacks and can, with maintenance use, provide disease control not possible with ICS and additional controllers. However, short-term and long-term adverse effects with systemic corticosteroids are frequent and often significant. Furthermore, recent studies indicate that short-term use of systemic corticosteroids, such as infrequent “bursts,” creates a more immediate risk for adverse effects, including metabolic, cardiovascular, thrombotic, and infectious events.^{10,11} Based on these newer observations and a longstanding knowledge of adverse effects with systemic corticosteroids, a major component of asthma treatment goals is to reduce the frequency of systemic corticosteroid use.

Three biologics, mepolizumab,³⁵ benralizumab,⁴⁶ and dupilumab,⁴⁷ have demonstrated oral corticosteroid–sparing effects without a loss of asthma control, and in some trials even improved outcomes. In VENTURE, a total of 210 patients underwent treatment randomization: 103 received dupilumab, 300 mg, after a 600-mg loading dose, every 2 weeks, or matched placebo.⁴⁷ Subjects were aged 12 years or older and had been receiving prednisone, 5 to 35 mg per day, for the previous 6 months. The patients were also receiving high-dose ICS, fluticasone or equivalent, 500 mcg twice daily plus up to 2 additional controllers. Eligible subjects had an FEV₁ less than or equal to 80% (or <90% for adolescents), but no enrollment requirement was set for baseline blood or sputum eosinophil values, or any other T2 biomarker (ie, FeNO or IgE). The primary end point in VENTURE was the percentage reduction in the oral glucocorticoid dose from baseline to between weeks 20 to 24 without a loss of asthma control.

In the presence of dupilumab, a significantly greater reduction in the oral glucocorticoid dose was found, and this reduction occurred without a loss of asthma control. In contrast, a significant improvement in FEV₁ values occurred despite the reduction in the glucocorticoid dose. Moreover, there was also a significant reduction in the annualized rate of severe asthma exacerbations by 59.3%. In analyzing predictive factors affecting the success of reducing the oral corticosteroid dose, the percentage reduction in oral glucocorticoid was similar in subjects with peripheral blood eosinophil values (≥ 300 cells/ μ L or <300 cells/ μ L or ≥ 150 cells/ μ L vs < 150 cells/ μ L). A lack of influence of peripheral blood eosinophils was similarly noted in relationship to a systemic corticosteroid reduction of greater than or equal to 50%, less than 5 mg/d, or total elimination by dupilumab.

A number of important observations are derived from these oral corticosteroid–sparing results. Despite the reduction in systemic

corticosteroids, asthma characteristics of severe disease were positively modified: reduced exacerbations, improved lung function, and improved symptom control. The benefits from reducing systemic corticosteroids by the addition of biologics raises the possibility that biologics, whether directed toward IL-5 or IL-4/IL-13 pathways, have greater specificity to inhibit mechanisms that are contributing to disease pathophysiology and severity than corticosteroids. These corticosteroid-sparing effects offer the potential or reflection, of disease modification. Therefore, the effects of systemic corticosteroids, while with some benefit, may be sufficiently ineffective on aspects of underlying inflammation in severe disease, thus leading to their limitations to the anticipated degree of asthma disease control.

The Influence of Comorbid Conditions in Selecting a Biologic

Illnesses, such as chronic rhinosinusitis with nasal polyps (CRSwNP), often increase asthma severity and efforts to achieve disease control; these interrelationships are particularly important in severe asthma. The development of CRSwNP usually begins in the third to fourth decades of life and can complicate existing asthma, both in terms of severity and responsiveness to existing treatments. In a portion of patients with CRSwNP, aspirin-exacerbated respiratory disease (AERD) also exists. The morbidity associated with CRSwNP is also significant, either by itself or in association with asthma, and there is a frequent need for systemic corticosteroids or surgical treatment in those affected.

Approaches to treatment of asthma in patients with CRSwNP plus or minus AERD, include high-dose ICS, leukotriene receptor modifiers, frequent bursts of systemic corticosteroids, and avoidance of nonsteroidal anti-inflammatory drugs. Histologically, nasal polyps are rich in eosinophils, suggesting a T2 pattern of inflammation. Dupilumab is approved for the treatment of CRSwNP and reduces the polyp size, diminishes mucous membrane thickening as noted on sinus CT scans, and restores the sense of smell.

In the LIBERTY NP SINUS-24 and LIBERTY NP SINUS-52 studies,⁴⁸ 59% ($n = 428$) of the total overall CRSwNP study population ($n = 724$) had asthma, not all of which was severe. Treatment with dupilumab significantly reduced the nasal polyp scores, nasal congestion indices, and the cumulative event rate: first systemic corticosteroid use or nasal polyp surgery (41.8/placebo vs 12.5/dupilumab), $P < .001$. In subjects with coexisting asthma, a 0.2 L improvement (0.13 L-0.29 L; $P < .001$) in FEV₁ occurred with dupilumab vs placebo along with a fall in ACQ-6 score of -0.82 (-0.98 to 0.67 , $P < .001$). The improvements in lung function occurred in the asthma group as a whole, not just in the severe portion of subjects.

Similarly, although not approved by the Food and Drug Administration (FDA) at present, mepolizumab's efficacy in CRSwNP has demonstrated a greater reduction in the need for surgery and clinical symptoms compared with placebo as well as reductions in polyp burden.^{49,50} Pooled analysis of the SIROCCO and CALIMA trials indicated greater efficacy of benralizumab every 8 weeks dosing in those patients with a baseline history of nasal polyposis as well.⁵¹ Similarly, post hoc analysis of pooled data from 2 BREATH studies in severe uncontrolled eosinophilic asthma revealed greater efficacy for reslizumab in patients with self-reported CRSwNP with or without AERD.⁵² Most recently, omalizumab was found to significantly reduce nasal polyps and congestion symptoms in adults with CRSwNP in 2 replicate phase III studies (POLYP 1 and 2).

In selecting a biologic in severe asthma, it is important and helpful to recognize that comorbid diseases may have significant influence on existing asthma severity and resulting disease burden. An awareness that treatment of CRSwNP improves asthma control may be a factor in selecting a biologic.

In addition to CRSwNP, other comorbid conditions can significantly affect asthma control, including chronic obstructive pulmonary disease (COPD, or Asthma-COPD overlap syndrome [ACOS]), obstructive sleep apnea, gastroesophageal reflux disease, vocal cord dysfunction, atopic dermatitis, chronic urticaria, eosinophilic granulomatosis with polyangiitis (EGPA), and hyper-eosinophilic syndrome. Some of the T2 biologics have garnered approval from the FDA for additional indications, whereas others have evidence-based data to support their use. Mepolizumab has been approved for use in EGPA at a higher 300-mg dose and would be an apt choice for a patient with EGPA and existing symptomatic asthma.⁵³ Mepolizumab has also been evaluated in COPD with an eosinophilic phenotype and found to be beneficial in reducing the annual rate of moderate to severe exacerbations in the METREX and METREO trials⁵⁴ and hence would be an appropriate consideration in patients with an asthma/COPD overlap and have an eosinophil phenotype. Omalizumab has been approved for use in chronic idiopathic urticaria (CIU) and would be an obvious consideration for those patients with severe asthma coafflicted with CIU. Omalizumab may also likely be the biologic of choice in a patient with asthma for whom immunotherapy (IT) is a treatment consideration, and there is an interest to prevent acute allergic reactions with an initiation of IT and achieve maintenance dosing with a greater degree of safety. Likewise, if moderate to severe atopic dermatitis is present, dupilumab would warrant being the choice as it is FDA-approved for that condition as well. Benralizumab has been evaluated in patients with symptomatic PDGFR α -negative hypereosinophilic syndrome (HES) and found to be efficacious in reducing eosinophil counts and leading to sustained clinical and hematologic responses and would be a logical consideration in those patients with this condition.⁵⁵

Steps in Selecting the Biologic for Individual Patients and Monitoring Effectiveness

The biologics available in severe asthma are directed toward patients with T2 inflammation. Biomarkers identifying these patients include peripheral blood eosinophils (≥ 150 cells/ μ L), FeNO (≥ 20 to 25 ppb), and IgE (≥ 30 IU/mL). At present, the selection of individual patients for a particular biologic based on these biomarkers is neither patient nor biologic specific. However, in the absence of measures for these biomarkers, it is unlikely that the available T2-directed biologics will be of potential benefit. A first step when considering a T2 biologic is demonstration of T2 inflammation with current biomarkers, peripheral blood eosinophils and/or FeNO. An example of a possible algorithm for biologic selection is shown below (Fig 4).²

Among the available biomarkers, peripheral blood eosinophils have been measured more frequently in clinical trials and are easy to assess. Given this level of experience and ease, peripheral blood eosinophils have a greater track record in predicting biologics selection and, most likely, warrant a higher placement on the hierarchy of biomarker profiling. However, eosinophil counts do not necessarily predict which of the biologics would be a better, or best, choice and FeNO may be a very direct and responsive, in some situations, measure to consider, particularly with an eventual wider spread use. Both peripheral blood eosinophils and FeNO provide essential data, but are largely threshold measures. Consequently, we are still in need of sophisticated algorithms and trial designs that use a combination of the available biomarker profiles in relationship to clinical attributes and outcomes to superstratify the patient populations to more precisely identify subphenotypes and endotypes that will guide choices of biologic therapies. The National Heart, Lung, and Blood Institute–sponsored PrecISE clinical research program has been conceived and designed with this very goal in mind to enroll patients who have been profiled with biomarkers and will then use an adaptive trial design to

provide precision medicine approaches for the management of patients with severe asthma (www.preciseasthma.org).

Comparative Evidence on Biologics

Head-to-head comparative studies of the biologics are not currently available to guide the selection of biologics for individual patients. Complex, indirect comparisons of available biologics using pooled data from existing studies and using similar cut-points for biomarkers have been performed and drawn varying conclusions. A recently published comprehensive review of biologics in the management of severe eosinophilic asthma by the European Academy of Allergy and Clinical Immunology illustrates insight into this approach as well, though it does not provide clear guidance as to which, when, or how to choose a biologic.⁵⁶ Thus far, only mepolizumab has an indication for use in the presence of peripheral blood eosinophilia as low as greater than or equal to 150 cells/ μ L. For those without eosinophilia, which likely reflects concurrent oral corticosteroid use, physicians need to reduce systemic corticosteroid dose to detect the reemergence of eosinophilia, an approach that has risks for provoking an asthma exacerbation. In contrast, the initiation of dupilumab in the presence of oral corticosteroid use does not have a requirement for the presence of eosinophils.

Choosing between the various IL-5 antagonists is difficult, as their effects on various clinical end points have proven to be similar. However, the threshold level of peripheral blood eosinophils for dosing is distinct: mepolizumab (≥ 150 cells/ μ L), benralizumab (≥ 300 cells/ μ L), and reslizumab (≥ 400 cells/ μ L). In addition, in this decision-making process, it is important to realize that the degree of effectiveness with the T2 biologics, including anti-IL-5 approaches, tends to be more pronounced with higher peripheral blood eosinophil counts.

Three recent indirect comparison analyses with complex methodologies have been published to help answer the question of whether one biologic is superior to another, often leading to varying conclusions. In an attempt to determine an indirect treatment comparison (ITC) between the 3 anti-IL-5 treatments, the effects of the 3 anti-IL-5s were compared at various levels of peripheral blood eosinophils. In the first ITC analysis, mepolizumab was deemed to be associated with notably significant improvements in clinically significant exacerbations and asthma control when compared with reslizumab or benralizumab in patients with similar blood eosinophil counts.⁵⁷ Casale et al⁵⁸ conducted a systematic literature review using the Markov Chain Monte Carlo simulation method and Bayesian statistical framework to compare reslizumab with benralizumab in similar patient populations (benralizumab subgroup with Eos >300 and reslizumab subgroup with Eos >400). This comparison suggested that reslizumab may be superior to benralizumab in terms of efficacy for patients with severe eosinophilic asthma with 2 or more exacerbations in the previous year when using GINA step 4/5 therapy.⁵⁸ Similarly, a network meta-analysis conducted by Ramonell et al⁵⁹ on the efficacy of the available biologics for management of severe eosinophilic asthma with an absolute eosinophil cutoff of greater than 250 revealed that all drugs were superior to placebo in preventing rates of asthma exacerbations with no interdrug differences noted, though dupilumab was noted to have the greatest magnitude of effect on rate of reduction of exacerbations. These are indirect comparisons as direct, head-to-head comparisons are not available or likely to happen anytime soon.

Summary data on relative exacerbation rates and asthma symptom scores was published by the Institute for Clinical and Economic Review and provides additional insight into the impact of biologics on clinical and economic metrics of T2-asthma (https://icer-review.org/wp-content/uploads/2018/04/ICER_Asthma_Final_Report_122018-1.pdf).⁶⁰ What is also lacking at present is a

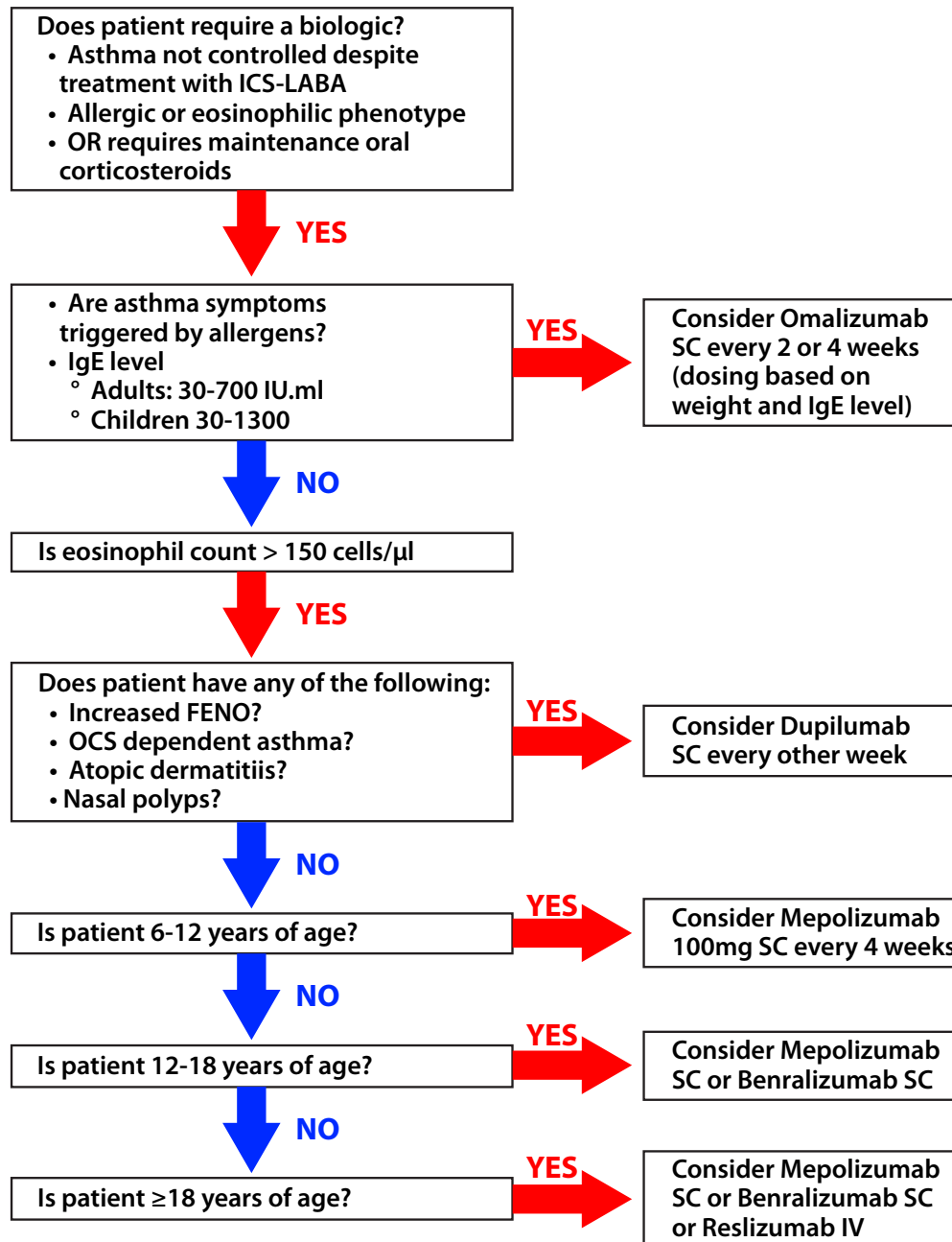


Figure 4. Suggested algorithm for decision-making processes in selecting a biologic for the treatment of T2 severe asthma. FeNO, fractional exhaled nitric oxide; ICS, inhaled corticosteroid; LABA, long-acting β -agonist; IgE, immunoglobulin E; OCS, oral corticosteroid; SC, subcutaneous.

cost-effectiveness and economic analysis of the biologicals as they are presently used in clinical practice because cost and coverage can be determinants in which biologic is chosen.

What would be particularly helpful, but largely absent at present, is a model or algorithm to predict an effective response early in the treatment phase with the selected biologic. To meet such a need, Bateman et al⁶¹ evaluated this possibility in 321 subjects treated with reslizumab for 52 weeks. The investigators developed a mathematical model, which compared changes from baseline with 16 weeks of treatment in ACQ and AQLQ scores, FEV₁ and the number of exacerbations in the first 16 weeks of treatment compared with the year before enrollment. These values were then appraised in relationship to outcomes achieved at 52 weeks. The calculated responses were categorized as responder, nonresponder, or indeterminate. The developed algorithm predicted responders,

and in 89.9% this prediction was correct. In a small number of subjects identified as nonresponders ($n = 26$), the prediction was correct 50% of the time. The investigators concluded that the algorithm was effective in predicting responders, but not nonresponders. These processes will be complex but are still a step in the right direction.

Conclusion

The emergence of biologicals has revolutionized the treatment of patients with severe asthma. Those affected patients with severe asthma continue to carry a heavy burden of disease and experience adverse effects despite receiving maximal therapy. A number of advances have begun to relieve the burden and yolk of severe asthma for many patients beginning with an identification of the

complex processes of airway inflammation and a recognition of key pathways that contribute to clinical manifestations of asthma as well as their features and characteristics. With this expanded knowledge, the technology to develop monoclonal antibodies applied, and with their availability, a demonstrated efficacy and safety, the T2 biologics have emerged and now are critical components of our therapeutic algorithm in severe asthma. The T2 biologics share similar targets, affect similar outcomes, for example, prevention of exacerbations and improved lung function and symptom control, and are the therapeutic products being considered for patients with severe asthma. Each has demonstrated a pattern of efficacy, with some commonalities and individual variations. A major and important clinical issue at present is selecting the biologic most likely to be effective in an individual patient. Algorithms are not available for the individual biologics at present. Our review has attempted to put into perspective the needs to be considered when a biologic is a next treatment choice, what experiences in determining clinical efficacy have been noted with the 5 biologics, and what characteristics have been observed with the individual biologics, and how these features may relate to the needs of particular patients. It is our hope that these analyses will assist the asthma caregiver in a more informed decision-making process when a biologic is being prescribed.

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