



Invited Review Article

Biological treatments for severe asthma: A major advance in asthma care[☆]William W. Busse^{*}

Department of Medicine, Division of Allergy, Pulmonary and Critical Care Medicine, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA

ARTICLE INFO

Article history:

Received 8 January 2019

Available online 18 February 2019

Keywords:

Asthma treatment

Biologics

Biomarkers

Severe asthma

Targets for biologics

ABSTRACT

Asthma is a heterogeneous disease with considerable variability noted in disease severity, patterns of airway inflammation, and achievement of disease control on current medications. An absence of disease control is most frequently noted in patients with severe asthma, and is defined as a lack of control while on high dose inhaled corticosteroids (ICS) plus a second controller medication. In part, this lack of control may relate to a diminished effect of current guideline-directed care on the existing pattern of airway inflammation in severe asthma.

Airway inflammation in severe asthma has been arbitrarily divided into T (type) 2 high and T2 low. T2 high is characterized by the generation of key cytokines, interleukin (IL)-4, -5 and -13, which generate and regulate airway inflammation. Biomarkers to mark the presence of T2-high inflammation include eosinophils, fractional exhaled nitric oxide (FeNO) and immunoglobulin (Ig) E, whose presence arises from the action of IgE, IL-5, IL-4, and IL-13. In this review, treatment of severe asthma with monoclonal antibodies, i.e. biologics, which are directed against these inflammation generated pathways are reviewed. The available monoclonal antibodies include omalizumab (anti-IgE); mepolizumab, reslizumab and benralizumab (anti-IL-5 pathways), and dupilumab (anti-IL-4/IL-13).

The use of these T2-high interventions has led to significant reductions in asthma symptoms, a decreased frequency of exacerbations, and improved lung function in many patients. Not only has the use of these monoclonal antibodies led to improved asthma control in patients with severe disease, their use has provided insight into mechanisms of severe asthma.

Copyright © 2019, Japanese Society of Allergy. Production and hosting by Elsevier B.V. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Introduction

Asthma is a heterogeneous disease in many respects: onset of disease, progression, inflammatory pathways, and, perhaps most importantly, response to treatment.¹ The heterogeneity of asthma was made clear in work by Moore *et al.*² who used detailed clinical phenotyping of subjects enrolled in the Severe Asthma Research Program (SARP) and the subsequent application an unbiased statistical approach to “group”, or cluster, evaluated subjects by common or shared clinical features. In her analysis, Moore *et al.*² identified five clusters of adult asthma patients with distinct,

though overlapping, clinical characteristics, largely reflecting disease severity and marked by increasing degrees of airflow obstruction and treatment levels to achieve disease control (Fig. 1). Of particular interest and relevant to this discussion were subjects in clusters 3, 4, and 5. Asthma participants in these clusters were taking high doses of medications, including inhaled corticosteroids (ICS) and additional controllers. In most cases, despite these high dose treatments, there was ongoing symptoms and frequent asthma exacerbations. These patients represent groups of asthma subjects who require high dose treatment to either achieve or maintain disease control. They are defined as having severe asthma and have become the patients under consideration for biological treatment.³

Current treatment centers on guideline-directed care and consists of a stepwise approach with increasing doses of medications, primarily ICS, often in conjunction with a second controller medication to achieve disease control.^{4,5} For most asthma patients, particularly those with mild-to-moderate disease, guideline-directed step care is effective, and adherence to treatment

[☆] Parts of this manuscript are from a previously published article, Biological treatments for severe asthma: where do we stand? *Curr Opin Allergy Clin Immunol* 2018; 18:509–18.

^{*} University of Wisconsin Hospitals and Clinics, 600 Highland Avenue, Madison, WI, 53792, USA.

E-mail address: wwb@medicine.wisc.edu.

Peer review under responsibility of Japanese Society of Allergy.

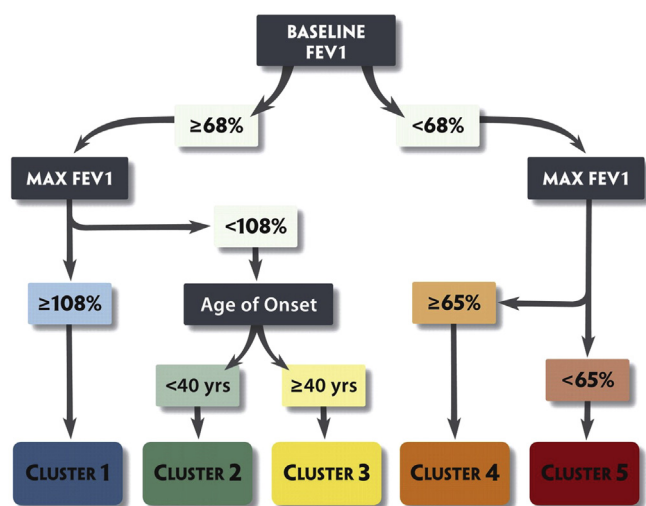


Fig. 1. Tree analysis of asthma clusters in SARP. Using three variables (baseline FEV₁ [with a bronchodilator withhold], maximal “Max” FEV₁ after six to eight puffs of albuterol, and age of onset of asthma), subjects can be assigned to the five clusters that range from milder asthma (Cluster 1) to more severe disease (Clusters 4 and 5). From Moore WC *et al.* Am J Respir Crit Care Med 2010; 181:315–23.

principles results in symptom control, prevention of exacerbations, and, importantly, an achievement of patient safety. In severe asthma, however, step care approaches in treatment are often ineffective, likely reflecting asthma heterogeneity and a treatment approach of “one-size fits all” is not effective in the presence of severe disease. These features of asthma in severe asthma result in diminished responsiveness to standard medications and need for alternative treatments with greater specificity for causes of existing disease severity.³

Airway inflammation determines disease characteristics as well as its severity and serves as a target for treatment. Inflammation in asthma is also heterogeneous (Fig. 2).⁶ Numerous cell types, mediators and immune pathways determine inflammatory pathway in asthma. The pathways are likely different in individual patients, vary over time and circumstances, and are more complex than a simple division into arbitrary groups: T (Type) 2 and non-T2 inflammation. More likely, the end product of airway inflammation will be an admixture of both pathways with either T2 or the non-T2 being dominant, and possibly reflecting a therapeutic target for greater disease control. As depicted in Figure 2, the process usually begins with the activation of the airway epithelium, which then sets into motion a cascade of events leading to eventual patterns of airway inflammation and clinical manifestations. Airway inflammation is considered to drive the alteration in airway pathophysiology including airway hyperresponsiveness and airflow obstruction. As noted, the pathway of inflammation has been arbitrarily divided into T2 high and non-T2. T2 inflammation is characterized by a predominance of eosinophilic inflammation, whereas non-T2 is marked by a neutrophilic cellular infiltrate or few cells – paucigranulocytic. It is important to re-emphasize that these classifications of the patterns of inflammation are arbitrary, and it is likely that mixtures of both pathways exist, at least to some degree, in most patients. However, as the T2 pattern is found to dominant in the majority of asthma patients, the development of novel treatments, especially biologics, have been focused on this component of the inflammatory pathways. Consequently, this discussion will focus on the use and effect of existing T2 biologics in asthma.

From the current understanding of T2 inflammation and likely importance of its components to these processes in asthma,

particularly severe disease, a number of pathways have drawn attention and led to the development of new targeted interventions. These include: (a) IgE, (b) eosinophils, and (c) the IL-4/IL-13 pathway. The approved biologics for asthma are directed towards these identified specific components of T2 inflammation and have emerged as important and effective treatments to improve asthma outcomes in severe asthma.

What steps need to be considered prior to the addition of biologics to asthma treatment?

Before biologics are added to asthma care, a number of steps in patient-specific characteristics need to be established.

Confirm the diagnosis of asthma

Before considering the addition of biologics, it is necessary to confirm that the patient has asthma. Although this seems to be an overly simplistic requirement, a significant portion of patients considered to have severe asthma do not have severe asthma or even asthma when a careful evaluations are performed.⁷ To further illustrate the importance of this requirement, Aaron *et al.*⁷ conducted a survey and subsequent evaluation of adult patients who had a diagnosis of asthma made in the past five years and were on treatment. 701 subjects were identified through a phone interview process in ten Canadian cities. In each individual recruited for study, asthma was confirmed by demonstrating FEV₁ reversibility or a positive response to methacholine. If these evaluations did not confirm asthma, the subjects were then evaluated by asthma specialists. Using this detailed and comprehensive approach, 33.1% of these subjects, who were receiving medication for asthma, did not have asthma. Despite what appears to be obvious clinical asthma requires confirmation by measures of pulmonary functions prior to moving forward to biologics. In addition, it is necessary to confirm that candidates for biologics do not have other forms of obstructive lung disease, like emphysema or chronic bronchitis, for which there is limited experience with these treatments.

Non-adherence to medications is common in any disease including asthma, and a lack of regular medication use contributes to ongoing symptoms and future risks for exacerbations.⁸ Furthermore, it is necessary to review techniques for medication use to ascertain whether proper inhaler procedures are followed for optimal delivery to the lower airway. Co-morbid conditions also may alter treatment responsiveness in asthma, including vocal cord dysfunction (VCD). VCD is often difficult to diagnosis or to separate its co-existence with underlying asthma. Reflux esophagitis frequently co-exists with asthma and may worsen asthma symptoms. Finally, approximately 20% of patients with asthma smoke, which also contributes to disease severity and a diminished responsiveness to ICS.³

Measure the biomarker profile

To help guide in the selection of biologics for severe asthma, a limited number of biomarkers are currently available: IgE, peripheral blood eosinophils, and exhaled nitric oxide (FeNO).^{6,9} Periostin has also been a validated marker of T2-high asthma and a gene product of IL-13 stimulation. However, measurement of periostin is influenced by bone metabolism, thus limiting its broad usefulness. The three biomarkers IgE, eosinophils, and FeNO, reflect the characteristics of the underlying inflammatory profile and, in particular, whether T2 inflammation may be present. Of these T2 biomarkers, experience with peripheral blood eosinophils has been greatest, perhaps reflecting the ease of this measurement and near universal involvement of eosinophils in T2 high inflammation.⁹

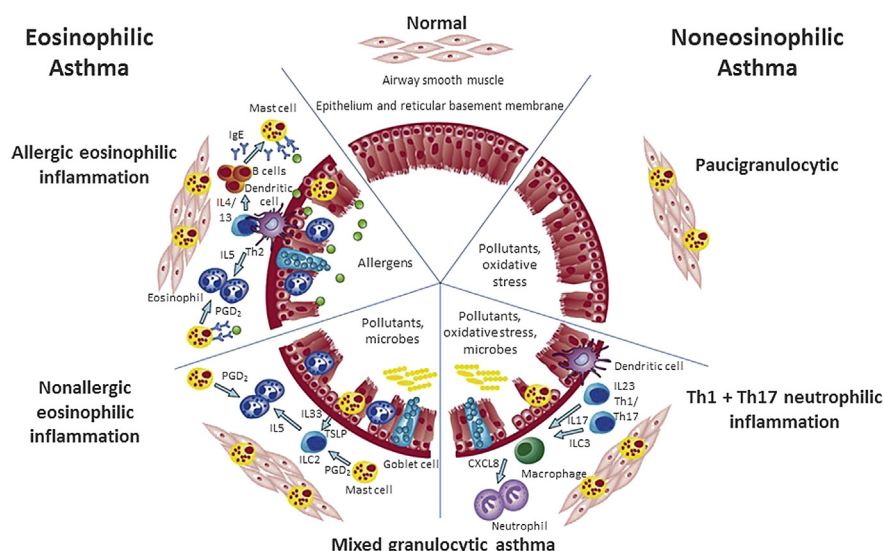


Fig. 2. Mechanisms and characteristic pathological features of asthma immunopathology. Features are divided into eosinophilic (allergic and non-allergic), non-eosinophilic (neutrophilic type 1 and type 17 and paucigranulocytic), and mixed granulocytic inflammation. IL, interleukin; TH, T helper; PDG2, prostaglandin D2; TSLP, thymic stromal lymphopoietin; ILC2, type 2 innate lymphoid cells; CXCL8, C-X-C motif chemokine ligand 8; ILC3, type 3 innate lymphoid cells. From Papi A *et al.* Lancet 2018; 391:783–800.³³

What has been the experience of biologics in severe asthma?

Omalizumab is a monoclonal antibody that binds to IgE to prevent it from combining with the high-affinity IgE receptor on mast cells and basophils, for example.¹⁰ This blocking effect prevents mast cell activation and subsequent generation of its inflammatory mediators when IgE is activated by allergens. Whether there are other IgE-binding cells whose function is inhibited by omalizumab is a current target of research. Omalizumab was the initial biologic approved for use in asthma. Prior to the approval of omalizumab, efficacy of asthma treatments was assessed primarily, if not exclusively, by an improvement of measures of lung function. Because omalizumab did not consistently improve lung functions, assessment of its efficacy needed to focus on another outcome that was, nonetheless, highly relevant to achieve disease control – exacerbations. Early clinical studies found omalizumab reduced the frequency of exacerbations, decreased the need for underlying medications, including ICS, but led to little improvement in lung functions when added to existing treatments.^{11,12}

Recognition that biological treatments could improve asthma control by reducing exacerbations was a major shift in treatment paradigms on how to assess and judge improved disease control. However, with increasing experience with this as a primary outcome, the importance of preventing exacerbations has become a principal target for biologics. The rationale for this approach is highly logical (Table 1). Omalizumab is now approved for use in asthma down to 6 years of age.

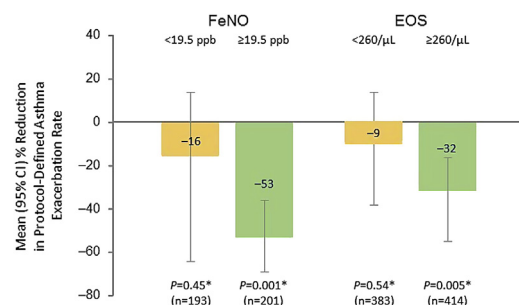
Table 1

Why are asthma exacerbations important and a primary treatment target?

- Major factor in asthma morbidity and mortality
- Significant contributor to cost
 - Emergency department care
 - Hospitalization
 - Patient productivity/societal costs
- Risk for progressive loss of lung function
- Exacerbations not always prevented by ICS/LABA
- Exacerbations are more frequent in severe disease
- Associated with common and frequent respiratory infections, rhinoviruses

In a large study of patients with documented severe asthma, Hanania and colleagues¹³ evaluated omalizumab in patients at GINA Step 4/5 treatment who required high dose ICS/LABA treatment but yet remained symptomatic with an ongoing risk for exacerbations. The addition of omalizumab to high dose ICS/LABA reduced asthma exacerbations by 25%; asthma exacerbations were defined as a loss of asthma control that resulted in the need for systemic corticosteroids. Interestingly, there was no effect of omalizumab on the frequency of exacerbations found in patients who were receiving maintenance oral corticosteroids. These results confirmed that, in severe asthma, omalizumab's benefit was on exacerbation-causing pathways and represented an outcome which did not appear to be affected by ICS/LABA. This large study in severe asthma confirmed earlier findings, which had been conducted prior to the accepted and wide-spread use of LABAs in combination with ICS to achieve disease control in patients with severe disease.

The same investigators evaluated the benefit of omalizumab on exacerbations in relationship, and hence guidance, to the presence of biomarkers for asthma: peripheral blood eosinophils and FeNO (Fig. 3).¹⁴ The cut points used in their evaluation were median



Greater prevention of exacerbations with omalizumab was seen in patients with high individual T2 biomarkers (EOS, FeNO)

Fig. 3. Mean percent reduction (95% CI) in protocol-defined asthma exacerbation rate in the low- and high-biomarker subgroups (baseline fractional exhaled nitric oxide [FeNO] and peripheral blood eosinophils). *Exacerbation reduction P values; omalizumab versus placebo in each biomarker subgroup. CI, confidence interval. Adapted from Hanania NA *et al.* Am J Respir Crit Care Med 2013; 187:804–11.

values of patients who had been enrolled in the clinical trial. If patients had elevated FeNO, ≥ 19.5 ppb (median FeNO value), omalizumab reduced exacerbations by 53%. In contrast, when FeNO was < 19.5 ppb, the prevention of exacerbations was only 19%. Similarly, in patients with eosinophil counts ≥ 260 cells/ μ L, exacerbations were reduced 32% by omalizumab, but only 9% when eosinophil values < 260 cells/ μ L. These analyses demonstrated that biomarkers are representative of T2 inflammation tracked with the achievement of greater clinical benefit from omalizumab. These data also suggest that these biomarkers would be helpful in selecting patients who are likely to get the greatest benefit from an anti-IgE treatment. Moreover, these results suggest that omalizumab's benefit is more likely to occur in the face of the T2-inflammatory response and also suggests an involvement of the T2 pathway as IgE contributes to the existing asthma.

Additional insights into the efficacy, and possible mechanisms of action of omalizumab have come from studies with asthmatic children. In 2011, Busse and Morgan published their findings from the Inner City Asthma Consortium (ICAC) trial in which omalizumab was evaluated in children 6–17 years of age with moderate-to-severe asthma and allergic sensitization.¹⁵ A one-year treatment with omalizumab vs. placebo was evaluated as an “add-on” to guideline-directed care. A key outcome in this group was a significant reduction in the frequency of asthma exacerbations. What was most interesting, and perhaps insightful to characteristics of benefit in the clinical risk and targeted mechanism of action, was a predominance of beneficial effects of omalizumab on seasonal asthma exacerbations: spring and fall. In North America, school-aged children have a well-demonstrated increase in asthma exacerbations when they return to school in the fall, e.g. the “September Epidemic of Asthma.”¹⁶ When the effects of omalizumab treatment were evaluated on an annual basis, i.e. January through December, the reductions of exacerbations were noted primarily during the spring and fall (Fig. 4).¹⁵ The relationship of the reductions of asthma exacerbations with omalizumab was most notable at times of high risk for children, e.g. when they returned to school after a summer vacation and were at an increased risk for colds. Nasal samples had been obtained and confirmed that the most likely cause of the seasonal asthma exacerbation was a rhinovirus upper respiratory infection.¹⁵

Although previous studies with omalizumab had clearly demonstrated the prevention of asthma exacerbations, the mechanisms of benefit with omalizumab had largely focused on IgE-

dependent processes given that IgE was its principal target. A return to school in the fall placed the high-risk asthmatic school-age children into two environmental situations which had the potential to affect control of their asthma: (1) high allergen exposure and (2) exposure to respiratory viruses. Rhinovirus was identified as the culprit event associated with an exacerbation. What was not determined is whether an enhancement of underlying allergic inflammation influenced the likelihood for a rhinovirus infection to cause an exacerbation. Evidence suggests that IgE is likely involved with both events, and through these dual beneficial effects reduces the risk for an asthma exacerbation.

To extend and expand on these observations, the Preventative Omalizumab or Step-up Therapy for Fall Exacerbations (PROSE) protocol was developed.¹⁷ PROSE was designed to test the hypothesis that pre-treatment with omalizumab prior to returning to school in the fall, and for the next 4-months, would prevent exacerbations at a high risk time of the year for respiratory tract illnesses and in a population of vulnerable asthmatic school-age children. School-aged children/adolescents (6–17 years of age) with moderate-to-severe asthma and a history of exacerbations were enrolled. The protocol had a number of key features as part of its design. For example, asthma control of the enrolled subjects was achieved and stabilized over a 4–9 month run-in period prior to randomization to receiving either placebo or omalizumab, both in conjunction with guideline-directed care, a month before their return to school. As hypothesized, the frequency of exacerbations occurring in the fall was significantly reduced by omalizumab.

The clinical trial experiences and open-label data with omalizumab indicate that it is an effective, safe, and anti-T2 inflammatory treatment of childhood and adult patients with severe asthma with underlying allergic sensitization. Based upon its longer term experience and extensive safety record for patients with allergic sensitization and severe asthma, omalizumab remains an initial biological treatment of choice.

A number of questions remain on the use of omalizumab including greater insight into its mechanisms of action. The principal clinical effects of omalizumab are its ability to reduce the frequency of exacerbations. In part, this may relate to alteration in IgE-activation of mast cells. There are other possibilities that involve IgE expression on other immune cells. There are data to indicate that some patients with asthma have defective anti-viral activity, which results from defective interferon generation.¹⁸ A series of studies from two laboratories have shown that IgE expression on mononuclear and dendritic cells reduces the generation of interferon- α from cells from asthmatic and allergic subjects during *in vitro* incubations with respiratory viruses.^{19,20} When IgE is removed from these cells, the generation of interferon- α during an incubation with respiratory viruses is normalized.

To determine if a reduction in cell-bound IgE during omalizumab treatment would have a similar effect on mononuclear cell generation of interferon- α , a cohort of PROSE participants had cells obtained prior to beginning omalizumab, or placebo, and at the end of the treatment period. Those children who had received omalizumab had a significant increase in the *in vitro* generation of interferon to a rhinovirus incubation. Moreover, subjects with the greatest restoration of interferon- α generation had significantly fewer exacerbations. These observations suggest, but do not prove, that a mechanism by which omalizumab reduces asthma exacerbations during a viral respiratory tract infection is a restoration of the anti-viral generation of interferon. Despite limitations associated with these data, our findings point to effects of omalizumab on cells other than mast cells or basophils, and effects that may serve to protect the host against a viral respiratory infection that ordinarily might have caused an asthma exacerbation.

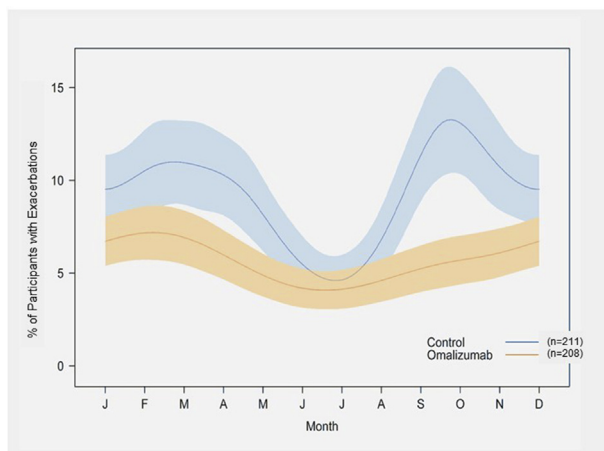


Fig. 4. Seasonal Variation in the frequency of exacerbations. The width of the bands represents the 95% confidence interval. Adapted from Busse WW, Morgan WJ *et al.* N Engl J Med 2011; 364:1005–15.

What are the experiences with anti-IL-5 pathway biologics in eosinophilic asthma?

Peripheral blood eosinophils are a biomarker for T2 asthma; the level of eosinophilia also reflects disease severity and risks for asthma exacerbations, thus suggesting that this cell is a participant in these phenotypic characteristics.⁹ Peripheral blood eosinophil values do not always parallel or reflect airway eosinophils, which are considered to be more reflective of this cell's involvement and participation in airway inflammation. However, the difficulty in routinely obtaining sputum samples to study lower airway samples prevents this approach from being readily available to most clinicians. Consequently, peripheral blood eosinophils remain an appropriate and convenient surrogate measure to verify the presence of eosinophilic asthma and a T2 pattern of the underlying inflammation.

The eosinophil has long been associated with asthma and its pathophysiology. The eosinophil's generation of inflammation contributes to the underlying airway disease and resulting altered pulmonary physiology.²¹ Eosinophil granules contain basic proteins which lead to airway injury and promote bronchial responsiveness. In addition, eosinophils can function as immunomodulator cells through the generation of a wide variety of cytokines including IL-5 which, in turn, can perpetuate eosinophilic involvement in asthma and create a vicious cycle. Much of the eosinophil's contribution to airway dysfunction in asthma comes from the actions of IL-5, which has become an effective target in therapy.

Two interventional strategies are available to regulate IL-5 and the eosinophil's participation in asthma, and presumably airway inflammation. One approach is a monoclonal directed against the cytokine IL-5 and the other, a monoclonal antibody that targets its receptor. IL-5 is a product of Th2 lymphocytes, innate lymphoid cells (ILC)-2, and mast cells, and plays a central role in regulating the terminal differentiation of eosinophils as well as participating in this cell's activation and recruitment to the airway. Mepolizumab and reslizumab are monoclonal antibodies directed against IL-5. By neutralizing IL-5, this cytokine cannot activate the IL-5R (receptor) on eosinophils. Benralizumab is a monoclonal antibody that is directed against the IL-5R; binding of benralizumab to the IL-5R activates antibody-dependent cell-mediated cytotoxicity (ADCC) to cause cell apoptosis. Both approaches are effective in reducing circulating eosinophils, and with a reduction in circulating eosinophils, fewer of these cells are available for migration to the airway. There is also evidence that the anti-IL-5 approaches reduce airway eosinophils.

Mepolizumab was the first anti-IL-5 antibody approved for use in asthma. In clinical trials, mepolizumab prevents asthma exacerbations, improves lung function, and reduces asthma symptoms. The dosing of mepolizumab (Nucala) has been established and is prescribed at 100 mg, given subcutaneously, every 4 weeks. This dose selection comes from the MENSA trial, which compared a 75 mg IV dose of mepolizumab with the currently prescribed 100 mg subcutaneous dose (Fig. 5).²² The study was designed to determine whether there was equivalence between the IV and the eventual subcutaneous dose of mepolizumab in reducing asthma exacerbations. Both mepolizumab doses were equivalent in preventing exacerbations and in the range of 50%. Also, studies have shown that for mepolizumab to be effective, patients need to have at least ≥ 150 eosinophils/ μ L and have uncontrolled disease at GINA Step 4/5.

The initial study to demonstrate the clinical benefit of mepolizumab was conducted by Haldar *et al.*²³ in a select population of well-defined and characterized patients with severe asthma. All enrolled subjects had uncontrolled asthma and a history of frequent annual exacerbations, approximately 5Xs/year. Despite the use of large doses of ICS and systemic corticosteroids in over

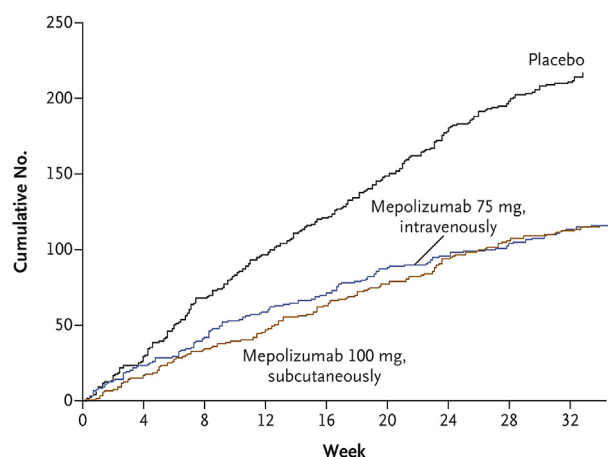


Fig. 5. Asthma Exacerbations at 32 Weeks. Asthma exacerbations in patients receiving either intravenous or subcutaneous mepolizumab or placebo. The rate of exacerbations was reduced by 47% (95% confidence interval [CI], 28 to 60) among patients receiving intravenous mepolizumab and by 53% (95% CI, 36 to 65) among those receiving subcutaneous mepolizumab, as compared with those receiving placebo ($P < 0.001$ for both comparisons). Adapted from Ortega HG *et al.* N Engl J Med 2014; 371:1198–207.

50% of the enrolled subjects, sputum eosinophilia (~6%) and peripheral blood eosinophils, over 300 cells/ μ L, were elevated. This degree of persistent eosinophilia is a key point in the selection of patients with severe but uncontrolled asthma. Early studies to evaluate mepolizumab had not included severe uncontrolled asthma who also had evidence of persistent eosinophils despite ongoing treatment. With these patient characteristics, mepolizumab reduced asthma exacerbations by 50%. The use of these inclusion criteria to demonstrate beneficial responses to anti-IL-5 treatment has been essential to see a clinical effect in subsequent clinical trials.

Reslizumab is also directed against IL-5 and predictably reduces circulating eosinophils. Reslizumab has two features that differentiates it from mepolizumab: (1) it is given intravenously (IV) and (2) dosing is weight based (3 mg/kg/every 4 weeks). In selecting eligible patients for treatment, reslizumab uses a “cut-off” value for eosinophils of 400 cells/ μ L and is a value that had been determined in its initial studies to see a beneficial outcome. At this blood eosinophil level, reslizumab reduced asthma exacerbations by approximately 50% and is similar, in this sense, to the effects of mepolizumab.²⁴ In subjects with peripheral blood eosinophils ≥ 400 cells/ μ L, reslizumab has also produced a 0.270 ± 0.1320 L improvement in FEV₁ over placebo in a 16-week trial.²⁵ Moreover, FEV₁ improved within 4 weeks of initiating treatment. When eosinophils were < 400 cells/ μ L, no improvement in lung function occurred with reslizumab.

Benralizumab has a distinct site of action and is directed against the IL-5R. Through this targeted action, benralizumab effectively reduces peripheral blood eosinophils. In two major trials, SI-ROCCO²⁶ and CALIMA,²⁷ benralizumab treatment was evaluated in large numbers of patients with moderate-to-severe asthma. These studies compared a 30 mg dosage every 4 or 8 weeks to placebo. In both trials, a significant reduction in asthma exacerbations of 45–51% occurred in patients with a peripheral blood eosinophil count ≥ 300 cell/ μ L (Fig. 6); FEV₁ values also significantly improved (Fig. 7).

Therefore, in patients with severe asthma, evidence of a peripheral blood eosinophil presence, and a lack of disease control on GINA4/5 treatment, eosinophil-depleting monoclonal antibodies are highly effective and reduce asthma exacerbations by approximately 50%. Greater precision in selecting anti-IL-5 treatment

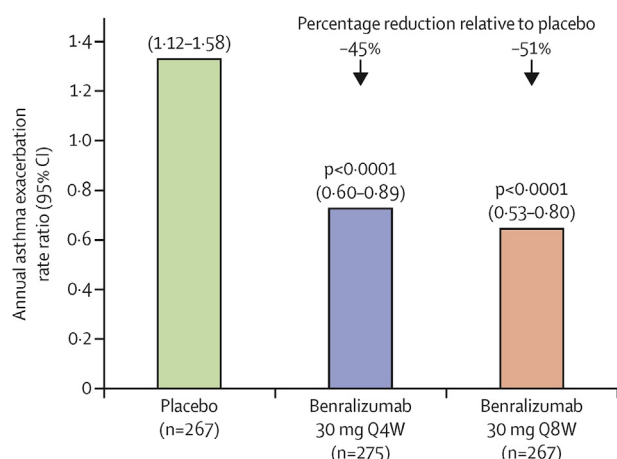


Fig. 6. Annual asthma exacerbation rate estimates at 48 weeks according to baseline blood eosinophil concentrations in relationship to placebo and benralizumab dosing (30 mg Q4W and 30 mg Q8W). Data for patients with baseline blood eosinophils ≥ 300 cells per μL . Estimates were calculated using a negative binomial model, with adjustment for treatment, region, oral corticosteroid use at time of randomization, and previous exacerbations. Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W). Adapted from Bleeker ER *et al.* Lancet 2016; 388:2115–27.

responsive patients other than on the basis of peripheral blood eosinophilia is not presently available.

All three anti-IL-5 pathway treatments lead to significant improvements in lung function. The mechanisms by which this improvement occurred were not established but a number of possible explanations exist. Many factors contribute to airflow obstruction in asthma including bronchospasm, inflammation, edema, remodeling effects, and mucus impaction of the airways. The anti-inflammatory effects of the anti-IL-5 pathway treatments have the potential to diminish existing airway inflammation, prevent progression of the loss of lung function that follows repetitive exacerbations, and possibly affect the presence of mucus formation.

Duncan *et al.*²⁸ used multidetector computer tomography lung scans to detect the presence of airway mucus in 146 subjects with varying severity of asthma and 22 controls. In the control subjects, there was little evidence of airway mucus; in contrast, airway mucus was detected in asthma but its presence varied widely. They also found that the level of mucus detected, zero, low and high,

related to the percent predicted FEV₁, with lowest FEV₁ values found in the presence of high mucus presence. There was also a correlation between sputum eosinophils and the mucus score. Through a series of *in vitro* studies, these investigators had findings to suggest that eosinophil activation and release of eosinophil peroxidase changed mucin into mucus plugs. These novel findings raise the possibility that a reduction in airway eosinophils could diminish the presence of mucus plugs and, with this change in airway mucus, improve lung function. Future work is needed to substantiate this possibility.

Patients with the most severe asthma often require sustained use of systemic corticosteroids (SCS) to maintain a level of disease control. Long-term use of SCS is, unfortunately, associated with significant adverse effects including weight gain, glucose intolerance, hypertension, and osteoporosis. Both mepolizumab and benralizumab have demonstrated an ability to reduce the need for SCS in this high risk, high morbidity population of asthma patients. Bel *et al.*²⁹ compared the corticosteroid-reducing effects of mepolizumab in 135 SCS-dependent patients and found treatment to lead to a 50% reduction in the need for glucocorticoids versus 0 in the placebo treated group. Equally important, mepolizumab reduced the risk for exacerbations by 32% despite the significant reduction in systemic corticosteroids, as well as improving symptom control.

Nair *et al.*³⁰ evaluated whether benralizumab treatment would significantly reduce the need for oral glucocorticoid use in 220 severe, eosinophilic asthma patients. Benralizumab treatment, over a 28-week period, reduced oral glucocorticoid doses by 75% compared to 25% in the placebo-treated arm. Like observations with mepolizumab, the corticosteroid reduction was associated with an annual exacerbation rate reduction of 55% over values observed with placebo treatment. No changes in FEV₁ values were found.

There are a number of clinical insights on the effects of an-IL-5 treatment from SCS reduction studies. Both studies demonstrated that anti-IL-5 pathway treatment diminished not only the need for systemic corticosteroids but also led to improved asthma outcomes. From my perspective, these results indicate that treatment directed towards a specific pathway of T2 inflammation, in this case, eosinophils, may be more effective than what is considered the most potent asthma therapy available – oral corticosteroids. Thus, not only may biologics reduce the potential for side effects from oral corticosteroid use, but, at the same time, improve asthma control. These findings suggest that when eosinophils continue to exist, despite guideline-directed care, biological treatment targets eosinophils and its resulting inflammation has greater effect because of its specificity for the airway inflammatory mechanisms.

There are different recommended requirements in the prescribing of anti-IL-5 pathway monoclonal antibodies for asthma that are dependent on the specific antibody. Mepolizumab is given subcutaneously, 100 mg/month, with a peripheral blood eosinophil count requirement of ≥ 150 cells/ μL . Reslizumab, in contrast, is given intravenously for patients with severe asthma whose eosinophil counts are ≥ 400 cells/ μL . Finally, benralizumab is given at a dose of 30 mg every 4 weeks, initially for 3 months at which time the dosing can be extended to every 8 weeks; it is for patients with blood eosinophils ≥ 300 cells/ μL . Therefore, selecting which anti-IL-5 pathway treatment will depend upon a number of factors including the blood eosinophil values of the patient. What has also been noted is a greater and more consistent response, e.g. reduction in exacerbations or improvement in FEV₁, in subjects with higher numbers of peripheral blood eosinophils. For the clinician to select which of the three anti-IL-5 antibodies to use for treatment, there needs to be an awareness of how baseline values of blood eosinophils will affect outcomes along with a convenience of dosing,

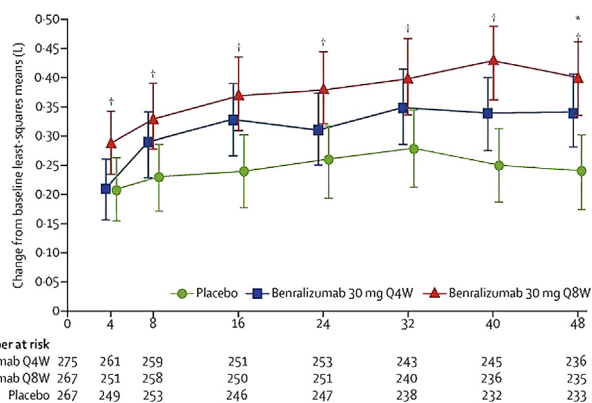


Fig. 7. Change from baseline in prebronchodilator forced expiratory volume in 1 s according to baseline blood eosinophil concentrations. Data for patients with baseline blood eosinophils ≥ 300 cells per μL . Q4W, every 4 weeks; Q8W, every 8 weeks (first three doses Q4W). *p < 0.05 for benralizumab 30 mg Q4W vs placebo. †p < 0.05 for benralizumab 30 mg Q8W vs placebo. Adapted from Bleeker ER *et al.* Lancet 2016; 388:2115–27.

concurrent use of systemic corticosteroids, dosing frequency, and route of administration – subcutaneous vs. intravenous.

At present, there are no direct comparisons of any of the biologics, including those of the anti-IL-5 pathway group. For many reasons, it is unlikely that direct comparisons will be available soon. In an attempt to determine comparative effects of mepolizumab, reslizumab, and benralizumab, an Indirect Treatment Comparison (ITC) analysis was conducted. In this analysis, we compared measured outcomes, reductions in exacerbations, improved lung function, and improvement in symptoms at various blood eosinophil values: ≥ 150 , ≥ 300 , and ≥ 400 cells/ μL . In addition, only licensed doses of these three biologics were compared. The rationale for this approach was stated above: The effect of treatment are often dependent on the eosinophil level and the effects of treatment vary on the outcome measured.

When an ITC approach was applied to clinically significant exacerbations, relative effectiveness could be estimated (Fig. 8). Although this approach does not replace direct comparisons, the use of an indirect assessment may provide guidance in the choice of the biologic most likely to provide benefit under conditions of eosinophil values in specific patients.

What experience has been gained with IL-4/IL-13 blockade?

IL-4 and IL-13 are also significant contributors to T2 inflammation in asthma (Fig. 2) and products of their action are associated with biomarkers as well. IL-4 causes an antibody isotype switch to IgE production which can then lead to allergen sensitization. IL-13 has numerous and significant effects on the airway as it stimulates

mucus production from goblet cells, promotes airway remodeling and affects airway smooth muscle contractility. IL-13 also acts directly on airway epithelium to generate FeNO. Finally, IL-13 is important in stimulating vascular adhesion molecules to direct eosinophil migration.

Dupilumab is a human antibody directed against the IL-4R (receptor) that also blocks IL-13 activation as well. Dupilumab is approved for use in atopic dermatitis and asthma in adults. Castro and colleagues studied dupilumab in 1900 patients, ≥ 12 years of age with uncontrolled asthma.³¹ Enrolled subjects demonstrated FEV₁ reversibility, persistent asthma symptoms (ACQ ≥ 1.5), and a history of an asthma exacerbation in the past year. The enrolled patients had measurements of FeNO and peripheral blood eosinophils prior to treatment. Dupilumab significantly reduced the frequency of asthma exacerbations by approximately 50% (Fig. 9). In addition, dupilumab significantly improved the FEV₁, an effect which began two weeks after initiating treatment (Fig. 10). In patients with eosinophils ≥ 150 cells/ μL and FeNO ≥ 25 ppb, dupilumab's efficacy was greatest in relationship to preventing asthma exacerbations and improving the FEV₁. In contrast, if eosinophils were < 150 cells/ μL and FeNO < 25 ppb, dupilumab did not have a significant effect on outcomes of lung function improvement or prevention of exacerbations. As anticipated, the presence of T2 inflammation appears necessary for dupilumab to improve asthma control, and peripheral blood eosinophils and FeNO are effective biomarkers to predict this response.

Rabe and colleagues³² evaluated dupilumab's ability to reduce the need for systemic corticosteroids. In 210 enrolled patients who required oral corticosteroids to maintain asthma control,

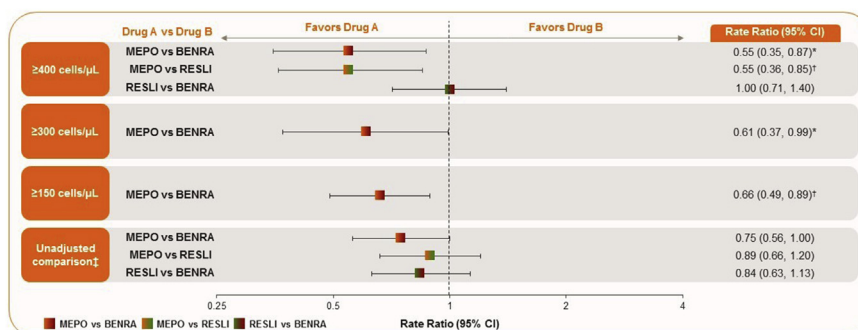


Fig. 8. Clinically significant exacerbations. Indirect comparisons of the rate of clinically significant exacerbations by baseline blood eosinophil subgroups and in the ITT population. * $p < 0.05$, † $p < 0.01$, ‡ Raw data that have not been adjusted for exacerbations and blood eosinophil threshold. Note: No comparisons with reslizumab were possible below 400 cells/ μL due to the inclusion criteria of those trials. BENRA, benralizumab; MEPO, mepolizumab; RESLI, reslizumab. Adapted from Busse W et al. J Allergy Clin Immunol 2019; 143:190–200.³⁴

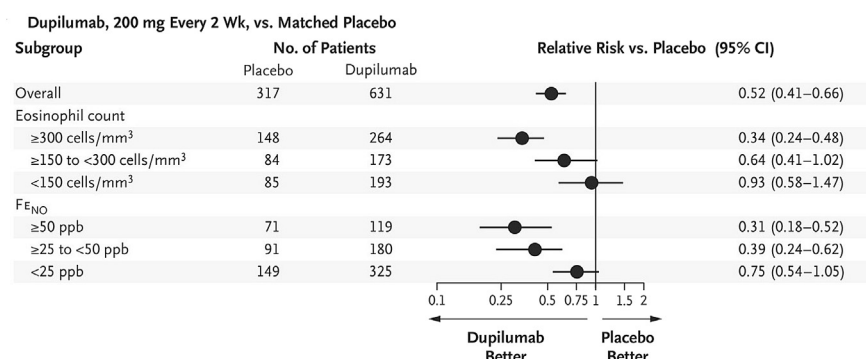


Fig. 9. Forest Plots of the Risk of Severe Asthma Exacerbations in the Intention-to-Treat Population and in Subgroups Defined According to Baseline Blood Eosinophil Count and Baseline FeNO in relationship to placebo and dupilumab (200 mg every 2 weeks). FeNO denotes fraction of exhaled nitric oxide, and ppb parts per billion. Adapted from Castro M et al. N Engl J Med 2018; 378:2486–96.

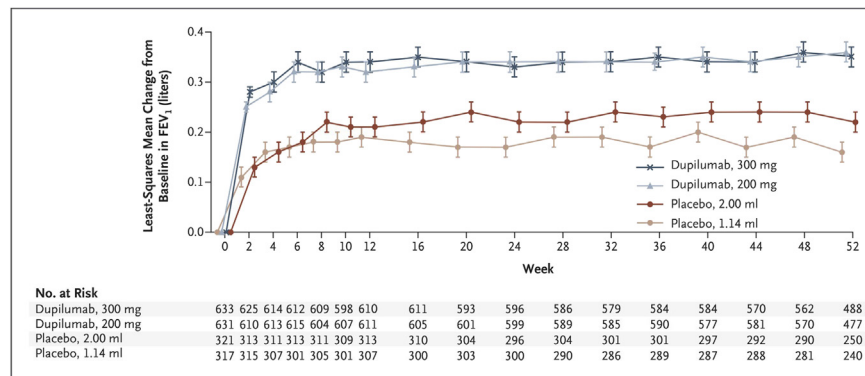


Fig. 10. Change in the Prebronchodilator FEV₁ from Baseline over the 52-Week Intervention Period in the Intention-to-Treat Population. Patients received dupilumab at a dose of 200 or 300 mg every 2 weeks or a matched-volume placebo. For the lower dose of dupilumab, the matched placebo had a volume of 1.14 ml. For the higher dose of dupilumab, the matched placebo had a volume of 2.00 ml. $P < 0.001$ for the comparisons of each dupilumab dose with matched placebo at week 12. I bars represent the standard error. FEV₁ denotes forced expiratory volume in 1 s. From Castro M *et al.* N Engl J Med 2018; 378:2486–96.

dupilumab significantly reduced the need for oral corticosteroids without a loss of asthma control. What was most insightful on the effects of dupilumab in this study population was a lower rate of asthma exacerbation despite the reduction of systemic corticosteroids by 59.3%. There was also improvement in lung function despite the reduction in oral corticosteroids.

A number of important conclusions can be gleaned from studies in which systemic corticosteroid use is reduced without a loss of asthma control but rather an improvement in outcomes, e.g. increased FEV₁ and reduced exacerbations. The improved asthma outcomes observed with dupilumab, mepolizumab and benralizumab, when systemic corticosteroids are reduced, suggest that the actions of these monoclonal antibodies have greater specificity and precision to regulate underlying inflammation, particularly T2 pathway disease, in patients where systemic corticosteroids are not effective. These findings suggest that a feature of severe asthma is a resistance, or reduced responsiveness, to the anti-inflammatory actions of corticosteroids. When interventions with treatments that have a greater precision for components of the T2-inflammatory pathways are used, asthma control improves.

Conclusion

The experiences of biologics that target T2 pathways represents a major advance in the treatment of severe asthma. The patient selection for biologics is necessarily guided by biomarkers, eosinophils and FeNO, both of which are helpful and necessary to identify patients likely to respond. These observations fit the paradigm that the T2 pathways contribute significantly to severe asthma, and the benefit from biologics in these patient populations occurs when treatment modifies inflammation associated with these pathways.

Where do we now stand with biologics in asthma? They are, at present, recommended for treatment of severe asthma when conventional treatment has not been effective. As severe asthma has the greatest clinical needs, this is a major advance. Their safety record, to date, has been reassuring though extensive monitoring of long-term administration is necessary. Therefore, for patients with severe asthma who do not achieve control with guideline-directed treatments, primarily high dose ICS, LABAs, and anticholinergics, biologics should be considered as the next treatment step when a biomarker profile is compatible with T2 inflammation exists. At present, non-type 2, or low-type 2, inflammatory profiles do not have specific therapies available.

The primary, and important benefit, of biologics in severe asthma has been an achievement of disease control, reflected by a significant reduction in exacerbations. The implementation of biologics in asthma treatment marks a new era in asthma treatment and provides effective options where nothing was previously available. The next steps with biologics will be to determine their efficacy in moderate disease, and eventually when safety issues are established, to determine disease modification or possibly asthma prevention.

Conflict of interest

The author reports personal fees from Boston Scientific, AstraZeneca, GlaxoSmithKline, Novartis, Sanofi/Genzyme-Regeneron, Teva, Genentech, Elsevier, and Medscape, e the submitted work.

References

- Wenzel SE. Asthma phenotypes: the evolution from clinical to molecular approaches. *Nat Med* 2012;18:716–25.
- Moore WC, Meyers DA, Wenzel SE, Teague WG, Li H, Li X, et al. Identification of asthma phenotypes using cluster analysis in the Severe Asthma Research Program. *Am J Respir Crit Care Med* 2010;181:315–23.
- Chung KF, Wenzel SE, Brozek JL, Bush A, Castro M, Sterk PJ, et al. International ERS/ATS guidelines on definition, evaluation and treatment of severe asthma. *Eur Respir J* 2014;43:343–73.
- National Asthma Education and Prevention Program. *Expert Panel Report: Guidelines for the Diagnosis and Management of Asthma*. Pub No. 91-3642. Bethesda, MD: National Institutes of Health; 1991.
- National Asthma Education and Prevention Program. *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma*. Bethesda, MD: National Institutes of Health; National Heart, Lung and Blood Institute; 2007. Pub No. 07-4051. Available from: <http://www.nhlbi.nih.gov/guidelines/asthma>. [Accessed 1 August 2011].
- Israel E, Reddel HK. Severe and difficult-to-treat asthma in adults. *N Engl J Med* 2017;377:965–76.
- Aaron SD, Vandemheen KL, FitzGerald JM, Ainslie M, Gupta S, Lemière C, et al. Reevaluation of diagnosis in adults with physician-diagnosed asthma. *JAMA* 2017;317:269–79.
- Bender BG, Pedan A, Varasteh LT. Adherence and persistence with fluticasone propionate/salmeterol combination therapy. *J Allergy Clin Immunol* 2006;118:899–904.
- Price DB, Rigazio A, Campbell JD, Bleecker ER, Corrigan CJ, Thomas M, et al. Blood eosinophil count and prospective annual asthma disease burden: a UK cohort study. *Lancet Respir Med* 2015;3:849–58.
- Schulman ES. Development of a monoclonal anti-immunoglobulin E antibody (omalizumab) for the treatment of allergic respiratory disorders. *Am J Respir Crit Care Med* 2001;164:S6–11.
- Busse W, Corren J, Lanier BQ, McAlary M, Fowler-Taylor A, Cioppa GD, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol* 2001;108:184–90.
- Soler M, Matz J, Townley R, Buhl R, O'Brien J, Fox H, et al. The anti-IgE antibody omalizumab reduces exacerbations and steroid requirement in allergic asthmatics. *Eur Respir J* 2001;18:254–61.

13. Hanania NA, Alpan O, Hamilos DL, Condemi JJ, Reyes-Rivera I, Zhu J, et al. Omalizumab in severe allergic asthma inadequately controlled with standard therapy: a randomized trial. *Ann Intern Med* 2011;**154**:573–82.
14. Hanania NA, Wenzel S, Rosen K, Hsieh HJ, Mosesova S, Choy DF, et al. Exploring the effects of omalizumab in allergic asthma: an analysis of biomarkers in the EXTRA study. *Am J Respir Crit Care Med* 2013;**187**:804–11.
15. Busse WW, Morgan WJ, Gergen PJ, Mitchell HE, Gern JE, Liu AH, et al. Randomized trial of omalizumab (anti-IgE) for asthma in inner-city children. *N Engl J Med* 2011;**364**:1005–15.
16. Johnston NW, Johnston SL, Norman GR, Dai J, Sears MR. The September epidemic of asthma hospitalization: school children as disease vectors. *J Allergy Clin Immunol* 2006;**117**:557–62.
17. Teach SJ, Gill MA, Togias A, Sorkness CA, Arbes Jr SJ, Calatroni A, et al. Pre-seasonal treatment with either omalizumab or an inhaled corticosteroid boost to prevent fall asthma exacerbations. *J Allergy Clin Immunol* 2015;**136**:1476–85.
18. Wark PA, Johnston SL, Bucchieri F, Powell R, Puddicombe S, Laza-Stanca V, et al. Asthmatic bronchial epithelial cells have a deficient innate immune response to infection with rhinovirus. *J Exp Med* 2005;**201**:937–47.
19. Durrani SR, Montville DJ, Pratt AS, Sahu S, DeVries MK, Rajamanickam V, et al. Innate immune responses to rhinovirus are reduced by the high-affinity IgE receptor in allergic asthmatic children. *J Allergy Clin Immunol* 2012;**130**:489–95.
20. Gill MA, Bajwa G, George TA, Dong CC, Dougherty II, Jiang N, et al. Counter-regulation between the FcεpsilonRI pathway and antiviral responses in human plasmacytoid dendritic cells. *J Immunol* 2010;**184**:5999–6006.
21. Holgate ST, Sly PD. Asthma pathogenesis. In: Adkinson Jr NF, Bochner BS, Burks AW, Busse WW, Holgate ST, Lemanske RF, et al., editors. *Middleton's Allergy: Principles and Practice*. 8th ed. Philadelphia, PA: Elsevier Saunders; 2014. p. 812–41.
22. Ortega HG, Liu MC, Pavord ID, Brusselle GG, FitzGerald JM, Chetta A, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med* 2014;**371**:1198–207.
23. Haldar P, Brightling CE, Hargadon B, Gupta S, Monteiro W, Sousa A, et al. Mepolizumab and exacerbations of refractory eosinophilic asthma. *N Engl J Med* 2009;**360**:973–84.
24. Castro M, Zangrilli J, Wechsler ME, Bateman ED, Brusselle GG, Bardin P, et al. Reslizumab for inadequately controlled asthma with elevated blood eosinophil counts: results from two multicentre, parallel, double-blind, randomised, placebo-controlled, phase 3 trials. *Lancet Respir Med* 2015;**3**:355–66.
25. Corren J, Weinstein S, Janka L, Zangrilli J, Garin M. Phase 3 study of reslizumab in patients with poorly controlled asthma: effects across a broad range of eosinophil counts. *Chest* 2016;**150**:799–810.
26. Bleecker ER, FitzGerald JM, Chanez P, Papi A, Weinstein SF, Barker P, et al. Efficacy and safety of benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting beta2-agonists (SIROCCO): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet* 2016;**388**:2115–27.
27. FitzGerald JM, Bleecker ER, Nair P, Korn S, Ohta K, Lommatzsch M, et al. Benralizumab, an anti-interleukin-5 receptor alpha monoclonal antibody, as add-on treatment for patients with severe, uncontrolled, eosinophilic asthma (CALIMA): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet* 2016;**388**:2128–41.
28. Dunican EM, Elicker BM, Gierada DS, Nagle SK, Schiebler ML, Newell JD, et al. Mucus plugs in patients with asthma linked to eosinophilia and airflow obstruction. *J Clin Invest* 2018;**128**:997–1009.
29. Bel EH, Wenzel SE, Thompson PJ, Prazma CM, Keene ON, Yancey SW, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med* 2014;**371**:1189–97.
30. Nair P, Wenzel S, Rabe KF, Bourdin A, Lugogo NL, Kuna P, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med* 2017;**376**:2448–58.
31. Castro M, Corren J, Pavord ID, Maspero J, Wenzel S, Rabe KF, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med* 2018;**378**:2486–96.
32. Rabe KF, Nair P, Brusselle G, Maspero JF, Castro M, Sher L, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med* 2018;**378**:2475–85.
33. Papi A, Brightling C, Pedersen SE, Reddel HK. Asthma. *Lancet* 2018;**391**:783–800.
34. Busse W, Chupp G, Nagase H, Albers FC, Doyle S, Shen Q, et al. Anti-IL-5 treatments in patients with severe asthma by blood eosinophil thresholds: indirect treatment comparison. *J Allergy Clin Immunol* 2019;**143**:190–200.