

Biologics in Asthma—The Next Step Toward Personalized Treatment

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Overall Purpose/Goal: To provide excellent reviews on key aspects of allergic disease to those who research, treat, or manage allergic disease.

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List of Design Committee Members: Jared Darveaux, MD, and William W. Busse, MD

Activity Objectives

1. To identify future and current treatment options for patients with asthma who are suboptimally controlled.
2. To describe how specific patient endotypes can direct selection of biological agents.
3. To describe the mechanisms of many of the monoclonal antibodies being developed for the treatment of asthma.

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Asthma is a multifaceted disease and is associated with significant impairment and risk, and a therapeutic response that is highly variable. Although current treatments are usually

effective for patients with mild-to-moderate disease, patients with more severe asthma are often unresponsive to current efforts, and there remains a need for agents with properties that may achieve control in these individuals. There is ongoing research to identify bioactive molecules that contribute to the pathophysiology of asthma, and many of these have been identified as potential therapeutic targets to improve control of this disease. As a consequence of these efforts, monoclonal antibodies have been developed and tested as to their effectiveness in the treatment of asthma. The assessment of these new treatments has identified particular pathways that, in selected patients, have shown benefit. The following review will discuss the current and future use of biological agents for the treatment of asthma, their efficacy, and how certain patient phenotypes and endotypes may be associated with biomarkers that may be used to select treatments to achieve greatest effectiveness of their use. As knowledge of the effects of these biological agents in asthma emerges, as well as the patients in whom they are most beneficial, the movement toward personalized treatment will follow. © 2015 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2015;3:152-60)

Key words: Asthma; Biologics; Therapeutics

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Abbreviations used

AQLQs- Asthma quality of life questionnaires
EPR3- Expert Panel Report 3
FEV₁- Forced expiratory volume in 1 second
F_ENO- Fractional exhaled nitric oxide
GM-CSF- Granulocyte-macrophage colony-stimulating factor
ICS- Inhaled corticosteroids
IFN-β- Interferon beta
IFN-γ- Interferon gamma
IL- Interleukin
LABA- Long acting beta agonist
SNPs- Single nucleotide polymorphisms
Th1- T helper 1
Th2- T helper 2
TNF-α- Tumor necrosis factor alpha
TSLP- Thymic stromal lymphopoietin

Guidelines for the diagnosis and management of asthma were established to provide an evidence-based approach for the treatment of this disease.¹ In the Expert Panel Report 3 (EPR-3), 6 treatment steps were identified and based on patients' disease severity, as reflected by symptoms, lung function, frequency of exacerbations, and response to treatment.¹ For the majority of patients with asthma, disease control is achieved within the first 3 treatment steps that include the use of inhaled corticosteroids (ICS) either alone or in combination with long-acting beta-agonists (LABA) or leukotriene receptor antagonist. This approach has provided a safe and effective mode of treatment.

When patients do not respond completely to these initial treatment choices, the approaches over the next 3 escalating steps is not always straightforward—a situation aptly captured in a recent editorial by Drs. Erika von Mutius and Jeffrey Drazen² where they said:

Asthma is both easy and hard to treat. It is easy to treat because the vast majority of patients with asthma require little medication for a lot of benefit. In a patient with asthma previously untreated with a controller (i.e., a medication whose primary mechanism of action is not acute bronchodilation), initiating therapy with a controller often results in an improvement in asthma symptoms and lung function and a reduced number of asthma exacerbations. In the language of current asthma thinking, this approach addresses both the impairment and risk domains of asthma treatment. Asthma becomes hard to treat when asthma control is not obtained with the health care provider's first choice of a controller; this usually means that treatment needs to be stepped up and leads to the question, "My patient needs more treatment, but what will offer the greatest likelihood of improvement?"²

For patients who fall into this therapeutic dilemma, the next choices are limited and have begun to extend into the use of biologics. Although the use of biologics in asthma is a relatively new effort, significant advances have been made, and with these advances has come the promise for a more personalized and, hopefully, effective treatment for selected patients, particularly those with more severe disease. The results of trials with biological treatments in asthma, and what direction they will provide for future treatment, are the basis of the following discussion.

WHAT ARE THE TREATMENT OPTIONS FOR THE "UNRESPONSIVE" PATIENT WITH ASTHMA?

Airway inflammation in asthma is complex, interactive, and redundant, as well as variable from patient to patient, and within individual patients (Figure 1). A wide variety of cells, inflammatory molecules, and resident airway tissues participate in the development, persistence, severity, and pattern of inflammation in asthma, and likely are critical determinants to the translation of various clinical phenotypes. Although these multiple pathways contribute to airway inflammation, injury, and repair, along with bronchial smooth muscle dysfunction, some of these inflammatory products are likely to have a more dominant role than others and may serve to contribute to the pathophysiology in selected patients. IgE production, eosinophils, mast cells, and subpopulations of lymphocytes (ie, Th2 [T-helper 2]), with an ever-expanding list of key cytokines, ie, interleukin (IL)-4, -5, -9, -13, and -33, have emerged as major contributors to the pathogenesis of asthma. Immune cells, such as Th2 lymphocytes, produce IL-5 to further promote eosinophil development, as well as IL-3, IL-4, IL-6, IL-9, IL-13, and granulocyte-macrophage colony-stimulating factor (GM-CSF), to enhance the inflammatory response.^{3,4} Also likely contributing are the recently discovered type 2 innate lymphoid cells. These nonspecific innate immune effector cells on stimulation with thymic stromal lymphopoietin (TSLP) and IL-33, produce Th2-associated cytokines such as IL-5, IL-13, and IL-4.⁵ It is postulated that these type 2 innate lymphoid cells, contribute to an allergen-independent eosinophilic asthma phenotype. IL-33 is a cytokine released by epithelial cells in response to damage and, in turn, stimulates production of IL-4 and IL-13 to promote IgE production, airway hyperresponsiveness, inflammation, Th2 lymphocyte development, and eosinophil migration.^{3,6,7} Based on this schema, a number of cytokines have been identified as intriguing potential therapeutic targets in asthma treatment, particularly for patients who are not responsive to usual medications.

A first step to try to modify the effects of these inflammatory pathway mediators has been the development of monoclonal antibodies that can "knock out" or perhaps, more appropriately, "knock down" these amplification steps and, hence, block inflammatory pathways that lead to ongoing disease and resulting symptoms. The experiences gained with these biological interventions have not only shed light on the contribution of various molecules to clinical asthma but also begun to provide the new avenues of treatment. Moreover, these experiences have begun to identify characteristics of patients most likely to benefit from more selective interventions. Consequently, the use of biologics in asthma is providing a road map to personalized treatment, which may, in turn, have greater specificity for mechanisms germane to an individual patient's disease expression.

IgE as a treatment target in asthma

Allergic sensitization is present in the majority of patients with asthma.^{3,8} Based on this close association with asthma, its likely mechanisms to disease, and a reasoned target of treatment, anti-IgE was an initial biological agent developed, and the only one currently approved in asthma. Omalizumab (Genentech, San Francisco, Calif/Novartis, East Hanover, NJ) is an injectable humanized monoclonal antibody directed against the Cε3 domain of IgE and prevents an interaction with its high-affinity receptor (FcεRI) on mast cells, basophils, eosinophils, Langerhans cells, and dendritic cells.⁹ Omalizumab is currently recommended for the treatment of patients (>12 years in the United States) with

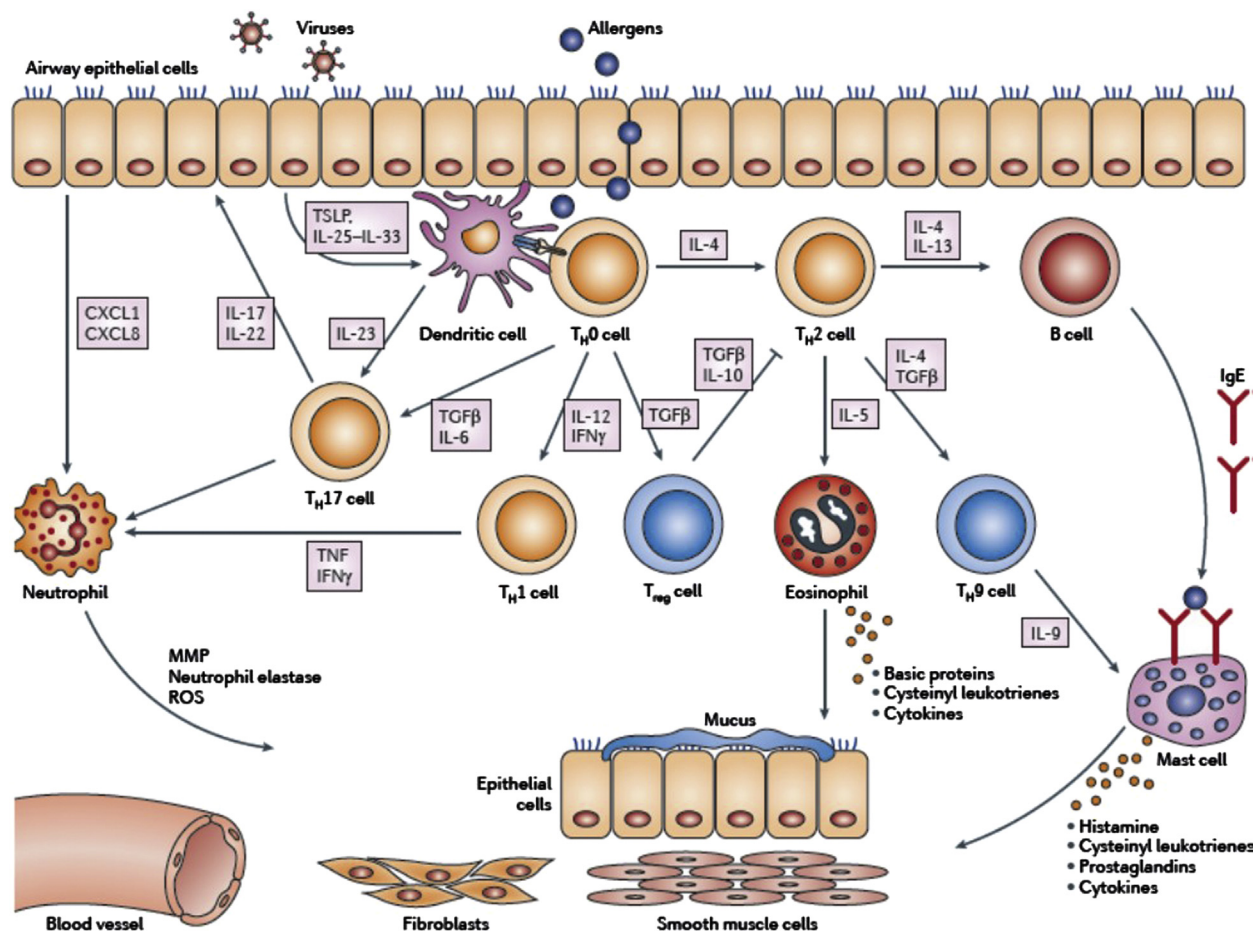


FIGURE 1. Pathobiology of asthma. Asthma originates from complex interactions between genetic factors and environmental agents such as aeroallergens and respiratory viruses. In particular, within the airway lumen, allergens can be taken up by dendritic cells, which process antigenic molecules and present them to naive T-helper (Th0) cells. The consequent activation of allergen-specific Th2 cells is responsible for the production of multiple cytokines and chemokines producing an allergic response. Adapted from Ref. 3.

moderate-to-severe allergic asthma, which is not adequately controlled by ICS, ICS+LABA, and, in some cases, oral corticosteroids, ie, EPR-3 steps 4-6.^{1,10}

In an initial proof-of-concept study, Fahy et al showed that omalizumab inhibited the early- and late-phase pulmonary responses to inhaled allergen in patients with allergic asthma.¹¹ Subsequent clinical studies found omalizumab-reduced symptoms, prevented exacerbations, allowed for a reduction in ICS use without a loss of asthma control,¹²⁻¹⁴ but had no effect on lung function.¹⁵ The beneficial effects of anti-IgE were found, primarily, in patients with more severe disease.¹⁶ Based on these results, the guidelines propose omalizumab for use in patients with severe disease who remain symptomatic despite high-dose ICS and LABA, or other controller medication.

Early studies with omalizumab preceded the availability of widespread use of ICS and LABA combination treatment. Consequently, to more fully and accurately assess the effects of omalizumab in patients at EPR-3 steps 5 and 6, Hanania et al¹⁴ enrolled patients 12 to 75 years of age with uncontrolled asthma despite the use of high-dose ICS and LABA combination therapy and, in some cases, a concomitant use of oral corticosteroids. Selected subjects were randomized into either omalizumab or placebo and treated for 48 weeks along with their medications.

The omalizumab-treated patients had a 25% relative risk reduction in asthma exacerbations. The effect of omalizumab on other outcomes, such as quality of life, symptom scores, and mean daily albuterol use, was less consistent. Furthermore, no significant reduction in asthma exacerbations occurred in patients who required systemic corticosteroids. These findings substantiated the benefit of omalizumab in severe asthma in adults as noted by Humbert et al.¹³

Subsequently, Busse et al evaluated the effect of omalizumab in an inner-city population of asthmatic children in a clinical trial that had a number of unique features.¹⁷ The recruited children were screened, found to have poor disease control, and then treated by a guidelines-based treatment algorithm. Subjects were evaluated every 2 months and adjustments were made to their medications to maintain control. Second, the study was conducted over a year to provide an opportunity to assess the effects of omalizumab on asthma exacerbations on a seasonal basis¹⁷ that, in this age group, tend to occur most frequently in the spring and fall, as the children return to school and develop a respiratory tract infection.¹⁷ Omalizumab nearly eliminated the spring and fall asthma exacerbations (Figure 2). These observations raise the possibility that IgE-dependent processes are risk factors for viral respiratory infections to provoke asthma

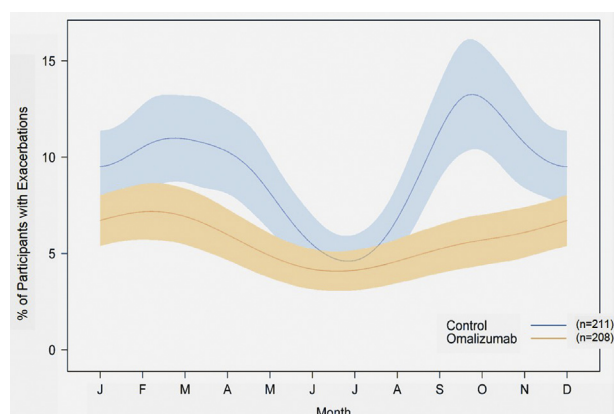


FIGURE 2. The seasonal variation in the percent of patients with asthma exacerbations and a comparison of guideline-directed care versus guideline-directed care plus omalizumab. Adapted from Ref. 17.

exacerbations; by reducing IgE levels, the probability that the likelihood for a respiratory virus to provoke an exacerbation can be attenuated exists.

A major question with the use of omalizumab, and other biologics, has been an identification of clinical characteristics to more specifically select patients for treatment. Although the patient selection for omalizumab has been based on IgE levels and the presence of antigen sensitization, these criteria have not been a reliable predictor of the treatment response.¹⁶ As a consequence, other biomarkers linked to asthma characteristics have been evaluated to predict the treatment outcomes with omalizumab. Th2 cytokine-driven inflammation is a known and predominant factor in allergic asthma.^{18,19} Fractional exhaled nitric oxide (F_{ENO}), peripheral blood eosinophil counts, and periostin are also markers frequently used to reflect the presence of Th2 inflammation.¹⁹ When Hanania et al evaluated whether these 3 biomarkers would predict treatment responses to omalizumab (Figure 3), asthmatic subjects with higher levels of F_{ENO}, blood eosinophil counts, and periostin had a greater reduction of exacerbations in response to omalizumab. This association has yet to be substantiated but may begin to provide a menu of biomarkers to more effectively select the most responsive patients for anti-IgE treatment.¹⁹

There has also been interest that omalizumab's effectiveness may extend beyond IgE-dependent asthma.²⁰⁻²³ Garcia et al evaluated 41 adult patients with severe, treatment-refractory, but nonatopic asthma. Omalizumab led to a significant reduction in FcεR1 expression on basophils (the primary outcome) and, in addition, increased FEV₁ (forced expiratory volume in 1 second) values.²⁴ Further study is needed to assess omalizumab's effect in settings where traditional IgE sensitization is not apparent.

Although omalizumab's effects have been centered on IgE-dependent processes, anti-IgE reduced the severity of chronic urticaria at treatment doses that were not based on serum IgE levels.²⁵⁻²⁷ Furthermore, the onset of beneficial effects with urticaria, in some patients, is rapid. In these studies, there was no evidence that IgE-dependent sensitization played a role in chronic urticaria. Therefore, omalizumab may have effects beyond allergen-IgE interactions.

Omalizumab is well tolerated.^{19,26,28,29} Initial concerns about an increased risk of malignancy associated with omalizumab use

have not been substantiated in larger patient databases.³⁰ A recent study that evaluated the long-term safety of omalizumab found no association with increased risk of malignancy.³¹ An increase in the frequency of anaphylaxis (0.09%) prompted an Omalizumab Joint Task Force to establish guidelines to enhance the safe administration of this medication.³²

The effect of eosinophil-directed treatment

Eosinophils are a frequent finding in asthmatic inflammation and have been felt to cause airway dysfunction secondary to a release of their proinflammatory cytokines, chemokines, lipid mediators, and cytotoxic granules from these cells.³³⁻³⁵ In addition, high blood eosinophils often reflect underlying airway inflammation and disease severity in asthma.²⁸ A reduction of sputum eosinophils by ICS reduces the frequency of exacerbations and usually indicates an establishment of disease control.³⁶ IL-5, a product of lymphocytes, mast cells, and, possibly, eosinophils,³⁶ contributes to terminal differentiation, survival, migration, and activation of eosinophils.^{3,36,37} Given the close association of eosinophils with asthma and this cell's dependence on IL-5, this cytokine has long been a primary target in asthma treatment.

In murine models of asthma, anti-IL-5 monoclonal antibodies blocked the increase in eosinophils and airflow obstruction following antigen challenge.³⁸ These animal studies gave great promise that anti-IL-5 would have a major effect on asthma. However, when studies with anti-IL-5 monoclonal antibodies were extended to human asthma, the initial results were disappointing.³⁷ Although the anti-IL-5 monoclonal antibodies reduced peripheral blood and sputum eosinophils, no effects on clinical features of asthma were seen.^{37,39} Nevertheless, the knowledge of eosinophil involvement in asthma, along with the potential to block IL-5, fueled further research, including a study by Flood-Page et al that showed a trend for mepolizumab to reduce exacerbations.³⁹

There are currently 3 anti-IL-5 monoclonal antibodies under investigation: mepolizumab (GlaxoSmithKline, Research Triangle Park, NC), reslizumab (Teva Pharmaceutical Industries, Petach Tikva, Israel), and benralizumab (AstraZeneca, Gaithersburg, Md). Collectively, these medications have a favorable safety profile and consistently reduce eosinophil counts.³ Mepolizumab is a humanized monoclonal antibody against IL-5.^{40,41} Several studies have evaluated the efficacy of mepolizumab in eosinophilic disorders and asthma where blood and sputum eosinophils remain despite ongoing treatment with corticosteroids. Rothenberg et al³⁵ showed that adult patients with a hypereosinophilic syndrome who received mepolizumab had a significant decrease in peripheral blood eosinophil levels and reduced need for prednisone to prevent relapses. Haldar et al studied mepolizumab in 61 patients with severe, treatment-refractory asthma with persistent eosinophilia.⁴⁰ Mepolizumab reduced the rate of exacerbation, corresponding to a relative risk of 0.57 compared with placebo (Figure 4). In addition, mepolizumab decreased blood and sputum eosinophil levels, as well as improved asthma quality of life questionnaires (AQLQs). However, there were no significant effects of mepolizumab on symptoms, FEV₁ after bronchodilator use, or airway hyper-responsiveness.⁴⁰ These observations pointed to the emergence of a personalized approach with mepolizumab to the treatment of patients with asthma with more severe disease and persistent eosinophilia, despite treatment, with the primary beneficial outcome noted in the domain of risks—a reduction in exacerbations.

The DREAM study extended these findings, but in a larger population, 621 subjects, with severe eosinophilic asthma, in

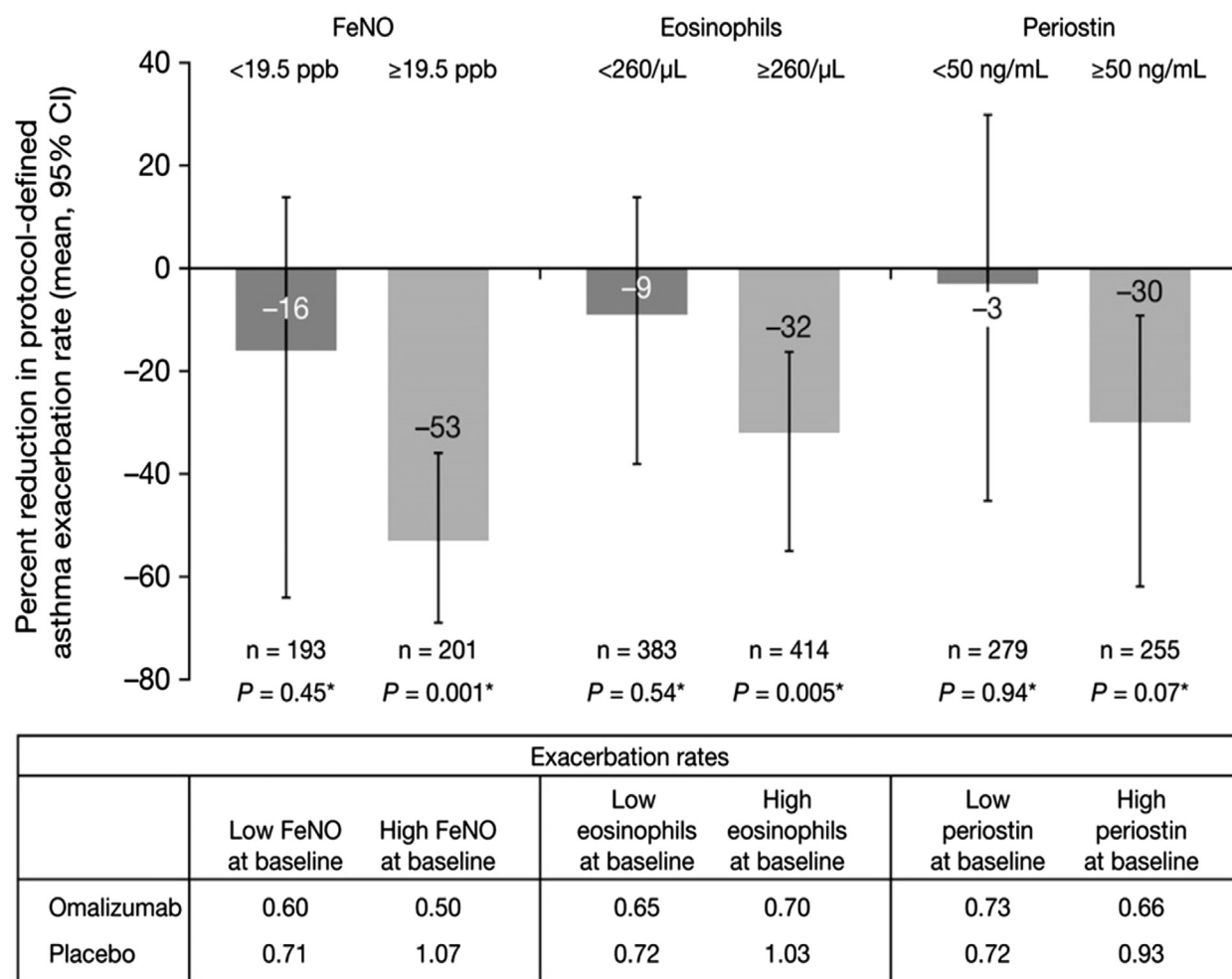


FIGURE 3. Mean percent reduction (95% CI) in protocol-defined asthma exacerbation rate in the low- and high-biomarker subgroups (baseline fractional exhaled nitric oxide [FeNO], peripheral blood eosinophils, and serum periostin). *Exacerbation reduction *P* values; omalizumab vs placebo in each biomarker subgroup. *CI*, confidence interval.¹⁹

patients aged 12-75 years, and also evaluated treatment with 3 doses of mepolizumab over 52 weeks. All 3 doses of mepolizumab led to a significant reduction in the frequency of exacerbations. As in previous studies, there was no effect on lung function. Although there were significant decreases in blood and sputum eosinophil levels with mepolizumab, there has been a less dramatic effect on airway tissue eosinophils that raises the question of the ability of an anti-IL-5 monoclonal antibody to reverse existing airway changes.³⁹ Interestingly, half of the participants in the DREAM study with eosinophilic asthma were not allergic.⁵ Neither atopic status nor IgE levels were associated with response to mepolizumab, which supported the notion that eosinophilic phenotypes of asthma may be fundamentally distinct from allergic asthma phenotypes.

Reslizumab is an IgG4/κ humanized monoclonal antibody also directed against IL-5.⁴² Castro et al evaluated reslizumab in 106 subjects with moderate-to-severe asthma and evidence of persistent eosinophils. Similar to findings with mepolizumab, reslizumab decreased blood and sputum eosinophils as well as improved AQLQs. However, unlike mepolizumab, FEV₁ and forced vital capacity values improved. This difference may be a reflection of patient selection. Patients evaluated in the DREAM

study were chosen based on markers of eosinophilic inflammation, whereas those in the reslizumab study were included with high sputum eosinophilia. Therefore, the reslizumab group may better reflect an eosinophilic asthma phenotype.

Finally, benralizumab is a humanized monoclonal antibody directed against the α-chain of the IL-5 receptor.^{36,43} Benralizumab is unique in that it not only blocks the effects of IL-5 on eosinophils, but actually results in eosinophil death through cell-mediated cytotoxicity.⁴⁴ Benralizumab produces a dose-dependent reduction in blood eosinophils. Remarkably, these effects can last up to 8-12 weeks after a single dose.⁴³ When studied in asthmatic subjects with sputum eosinophilia, benralizumab showed a significant reduction in sputum and airway mucosal eosinophils, and a 100% reduction in blood eosinophil counts.³⁶ The effects of benralizumab in asthma are undergoing evaluation.

A consistent feature of antieosinophilic treatment in asthma has been a reduction in exacerbations. Furthermore, the effects of IL-5 modulation appear to be limited to patients who are already on corticosteroid treatment, yet have persistent eosinophilia despite corticosteroids and continue to experience exacerbations. However, the most impressive beneficial results have been seen in those patients with significant peripheral blood eosinophilia at

baseline. The observations with antieosinophilic treatment also point to patient-specific characteristics in whom this class of biologics is able to show an effect—personalized treatment.

IL-4- and IL-13-related antibodies

IL-4 is one of several cytokines critical for the differentiation of CD4⁺ lymphocytes into Th2 cells^{6,18} and the induction of B-cell isotype switching to increase IgE production and to up-regulate IgE receptors, the expression of vascular cell-adhesion molecule 1, eosinophil transmigration into the lungs, inhibition of T-lymphocyte apoptosis, and mucus secretion. IL-4 further influences this Th2 effect by inhibiting production of the Th1 cytokine interferon (IFN)- γ .^{6,17} Approaches to reduce IL-4 activity have included an anti-IL-4 antibody, soluble IL-4 receptor, IL-4 transcription inhibitors, and IL-4/IL-13 receptor antagonists.⁶

Altrakincept (Immunex, Seattle, Wash) is a soluble recombinant human IL-4R that consists of the extracellular portion of the α -chain of the IL-4 receptor, and binds to IL-4 to inhibit its activity by blocking attachment to membrane-bound IL-4 receptors.⁶ Early clinical trials found soluble IL-4R safe and well tolerated. When studied in patients with moderate asthma, altrakincept maintained lung function after withdrawal of ICS.⁶ These effects could not be reproduced in later studies.³

Pascalizumab (Facet Biotech, Redwood City, Calif) is another humanized monoclonal antibody directed against IL-4 to prevent binding to its receptor.⁴⁵ Although pascalizumab was safe and well tolerated, it failed to show efficacy in symptomatic, corticosteroid-naïve patients with asthma.^{6,45}

IL-13, like IL-4, is integral to the Th2 response, and although produced mainly by Th2 T-cells, eosinophils, natural killer cells, and a recently discovered innate immune cell termed nuocytes have also been identified as a source of this cytokine.^{46,47} IL-13 works in concert with IL-4 to influence airway inflammation and remodeling, mucus production, IgE synthesis, and recruitment of eosinophils and basophils, as well as proliferation of bronchial fibroblasts and airway smooth muscle cells.³ Further evidence of involvement of IL-13 in the Th2-type response has been seen in patients with single nucleotide polymorphisms (SNPs) in the encoding IL-13. This SNP is also associated with increased eosinophils, serum total IgE, and asthma exacerbations.⁴⁸

Several monoclonal antibodies directed at IL-13 have been evaluated in human asthma models and were safe and well tolerated.^{3,49,50} In a randomized, double-blind, placebo-controlled study that involved 219 adult atopic asthmatic patients, who were uncontrolled with ICS therapy, lebrikizumab (Genentech, San Francisco, Calif) improved FEV₁ values by 5.5% compared with placebo. Subgroup analyses were also performed using periostin, which is generated by IL-13 from airway epithelial cells, as a marker to identify a “high Th2” phenotype. Within the high periostin subgroup, a more dramatic improvement in FEV₁ was seen, an increase of 8.2% at 12 weeks (Figure 5, panel B).⁵⁰ This finding suggests that periostin may be a useful biomarker to identify patients who belong to a Th2 phenotype and predictive where IL-13 contributes to asthma.

IMA-638 and IMA-026 (Pfizer, Groton, Conn) are IL-13 neutralizing antibodies that bind to the α -epitopes on the IL-13 molecule and prevent attachment to IL-13R α .⁴⁹ When studied in patients with mild atopic asthma, IMA-638 inhibited the early- and late-phase asthma response to an allergen challenge. Neither agent provided significant changes in allergen-induced airway hyperresponsiveness, serum IgE levels, or sputum eosinophil levels.⁴⁹ IMA-026, however, failed to achieve any clinical benefit in asthma trials.

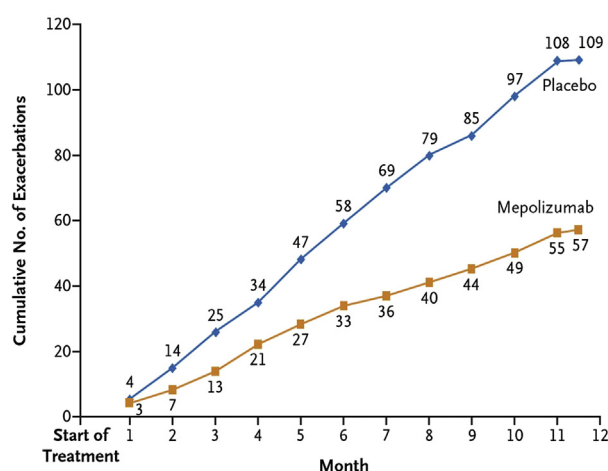


FIGURE 4. Mepolizumab and exacerbations of refractory eosinophilic asthma. The cumulative number of severe exacerbations that occurred in each study group over the course of 50 weeks. Adapted from Ref. 40.

The outcomes with individual IL-4 and IL-13 blockage have, other than lebrikizumab, been limited. The overlapping actions of these two cytokines bring into question the potential effectiveness of blocking of either of them individually. IL-4 and IL-13 receptors can be divided into type I and type II IL-4R α complexes. Type I receptor complexes exclusively bind IL-4, whereas type II receptor complexes contain an additional binding site for IL-13 (IL-13R α 1). This property allows type II receptor complexes to produce similar downstream signals by binding either IL-4 or IL-13⁵¹ and provides an avenue to develop therapies aimed at inhibiting the actions of both IL-4 and IL-13.

Pitrakinra (Aerovance, Berkeley, Calif) is an IL-4 variant that competitively inhibits IL-4 and IL-13 by binding to IL-4R α receptor complexes to block attachment of IL-4 and IL-13. Pitrakinra can be given by the subcutaneous and nebulized route. Pitrakinra reduced the late-phase fall in FEV₁ to an allergen challenge, and also reduced baseline levels of F_{ENO} after 4 weeks of nebulized treatment. However, no effect was seen on the early response to allergen challenge, and F_{ENO} increased after allergen challenge. This lack of effect on early response suggested its actions related to suppression of inflammation induced by IL-4 or IL-13 and not effects on mast cell function. Pitrakinra failed to prevent the postallergen-induced increase in airway hyperresponsiveness.¹⁸ Although pitrakinra has shown promise for treatment of atopic asthma, the translation to clinical asthma has yet to be established.

AMG 317 (Amgen, Thousand Oaks, Calif) and dupilumab (Sanofi, Bridgewater, NJ/Regeneron Pharmaceuticals, Tarrytown, NJ) are humanized monoclonal antibodies directed at IL-4R α to prevent the binding of IL-4 and IL-13.^{52,53} AMG 317 was studied in patients with moderate-to-severe asthma, was safe and well tolerated, but failed to meet its primary endpoint, an improvement of asthma symptoms. Although the time to an asthma exacerbation and the number of exacerbations that occurred were reduced, these findings were not statistically significant.⁵² In a *post hoc* analysis, patients with higher baseline symptoms received the most benefit, suggesting the potential need to select patients to see an effect.

Dupilumab was studied in patients with moderate-to-severe asthma who also had peripheral blood or sputum eosinophilia

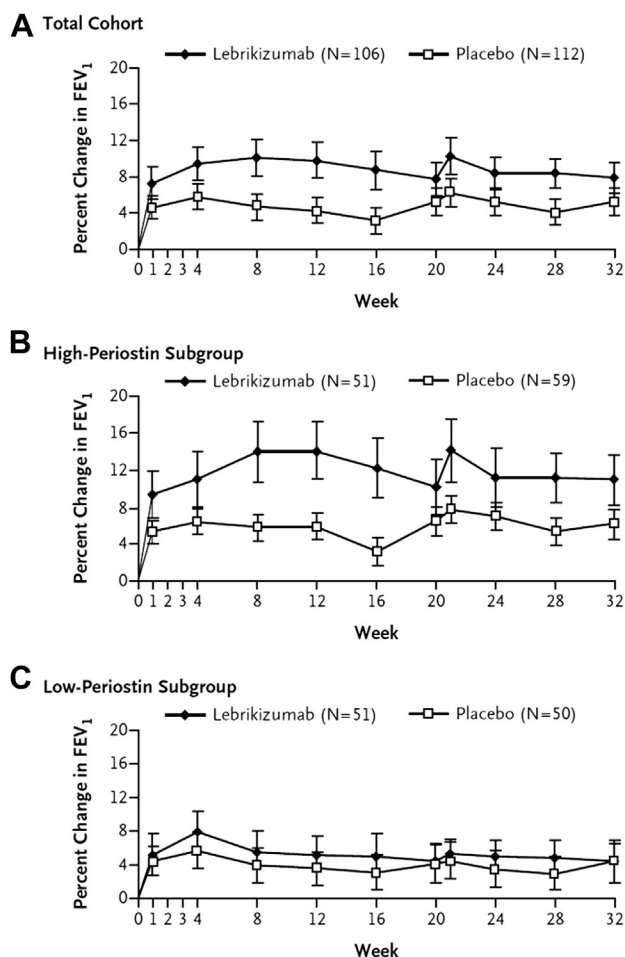


FIGURE 5. Relative change in forced expiratory volume in 1 second (FEV1) in the intention-to-treat population.

despite treatment with ICS and LABA.⁵³ After treatment stabilization, patients discontinued LABAs at week 4 and then began to taper and discontinue ICS. After 12 weeks of treatment, dupilumab-treated subjects had an 87% reduction in exacerbation frequency, as well as significant improvements in most measures of lung function and asthma control. In addition, subjects in the active treatment group had reduced levels of Th2-associated inflammatory markers.⁵³ For example, F_{ENO} was reduced after 4 weeks of treatment and remained low after discontinuation of ICS. Interestingly, some patients treated with dupilumab had large increases in peripheral eosinophilia.⁵³ The exact mechanism of this finding is not fully understood. One possible explanation is that because IL-4 and IL-13 recruit and facilitate eosinophil migration into the tissues, blockade of this pathway leads to an accumulation of eosinophils in the peripheral blood. No deleterious effects were seen in these individuals; however, this may need to be an area of focus in future studies. Although further study is necessary to establish long-term safety and effectiveness, this study has provided insight into the potential of agents that block the Th2 response via attacking both IL-4 and IL-13 activities. Furthermore, the clinical effect was “broad-based” with improvement noted on symptoms, lung function, and exacerbations.

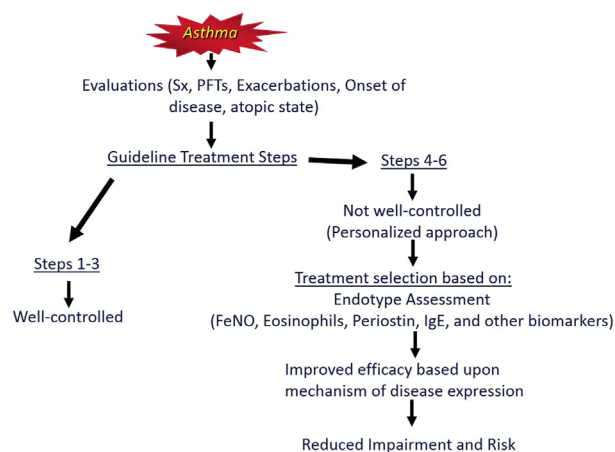


FIGURE 6. Individualized management for asthma. If control is not achieved with ERP3 steps 1-3, the assessment of asthma phenotype should guide selection of the most likely effective biological agent.

Other agents

There have been other agents that theoretically could improve outcomes in a chronic inflammatory condition such as asthma. Tumor necrosis factor alpha (TNF- α) recruits eosinophils and neutrophils to the airways by upregulating adhesion molecules.⁵⁴ When studied in asthma, anti-TNF- α agents produced conflicting results. Infliximab (Janssen, South Raritan, NJ) and golimumab (Janssen) are monoclonal TNF- α blocking antibodies. When studied in asthma, there were initial encouraging results that showed decreased exacerbations in mild-to-moderate asthma.^{55,56} However, later studies found no benefit on exacerbations or lung function.³ In addition, there was concern for the safety of these agents as noted with an increased risk for respiratory infections and cancer.

MT203 (Takeda, Deerfield, Ill) is a monoclonal antibody directed against GM-CSF. As GM-CSF is a growth factor involved in eosinophil survival and differentiation, it was thought that MT203 could potentially mitigate the effects of eosinophils.^{57,58} Murine models found antiinflammatory effects, and, in addition, MT203 decreased the survival of human eosinophils.⁵⁸ Further study is needed to determine the efficacy of MT203 in asthma and to identify which asthma populations are most likely to benefit from this product.

TSLP is an IL-7-like epithelia-derived cytokine produced in response to proinflammatory stimuli.^{59,60} It acts by inducing the release of Th2-related cytokines.⁶¹ Patients with asthma have elevated levels of airway TSLP,⁶¹ with the degree of elevation correlating to disease severity.⁶⁰ In fact, studies have shown that polymorphisms in the TSLP locus have a protective effect from asthma, atopic asthma, and airway hyperresponsiveness.⁵⁹ AMG 157 (Amgen) is a fully humanized anti-TSLP monoclonal antibody that binds TSLP to prevent an interaction with its receptor. When studied in subjects with mild allergic asthma, AMG 157 attenuated the early- and late-phase allergen-induced asthmatic responses. Most interesting and surprising, anti-TSLP also significantly reduced blood and sputum eosinophils and F_{ENO} .⁵⁹ Analysis of these data suggests, largely for the first time, that a biologic may affect underlying allergic inflammation in addition to blocking the response to an inhaled allergen. Safety and efficacy studies with AMG 157 are ongoing in the United States.

Other different phenotypes of asthma have carved a path for future research. Neutrophilic asthma has cultivated interest in targeting IL-17, IL-24, and IL-27. Epithelial cell involvement in asthma has sparked research into IL-25, IL-33, and IFN- β as potential targets.

Biologics in children. Most of the data to date on these agents have been restricted to study adult populations, particularly studies undertaken in the United States. However, there are data as to their utilization in the pediatric population as some biologics have been approved for use in Europe for several years. Omalizumab has the most abundant data as to its efficacy in children and is approved down to the age of 6 years in Europe. In a review of the evidence from the IA-05 trial submitted by Novartis Pharmaceuticals UK Ltd. to the National Institute for Health and Clinical Excellence, omalizumab was found to reduce the number of clinically significant exacerbations in children with severe persistent asthma on high-dose ICS/LABA therapy. However, there was no significant difference in severe exacerbations, hospitalizations, or asthma-related mortality. Moreover, the absolute reduction in exacerbations was small, with the greatest benefit found in children who had 3 or more exacerbations per year. Further study of these data found that the small improvement in quality-adjusted life-years was not sufficient to compensate for the high treatment cost.⁶² It was, therefore, concluded by the FDA that omalizumab should not be recommended in this population.⁶³

Contrary to these findings, as mentioned previously, Busse et al showed a dramatic decrease in spring and fall exacerbations in inner-city children with poorly controlled asthma, which indicates that IgE may play a role in seasonal exacerbations induced by upper respiratory infections.¹⁷ Current studies are being conducted to further evaluate not only the efficacy of omalizumab in children but also mRNA as a potential biomarker to predict response.

Of the other biologic agents, there is a paucity of data as to their use in the pediatric population. Those directed at eosinophils have ongoing studies, which are not limited to eosinophilic asthma. Mepolizumab and reslizumab have been studied in the treatment of eosinophilic esophagitis in children.⁶⁴⁻⁶⁶ Like studies in adults, mepolizumab has reduced eosinophil counts⁶⁴; however, the effect in eosinophilic asthma in the pediatric population has yet to be evaluated. The DREAM study (mentioned above) included children aged 12-17 years; however, the response in this subgroup was not presented.⁴¹ Reslizumab has previous and ongoing studies in eosinophilic asthma that include the 12-17 age group⁴²; however, like mepolizumab, specific analyses of this subgroup have not been presented.

The use of these agents in children in the United States will require further investigation of safety and efficacy. Although there is no absolute timeline as to the release of these agents, many experts believe that we will likely see their use in the next 5-10 years.

CONCLUSIONS

A significant proportion of patients with asthma do not achieve disease control on current treatments. In addition to the one biological asthma treatment in current use, omalizumab, others are undergoing clinical trial and many show considerable promise in selected populations of patients. Furthermore, insight and information into which patient or patient populations are likely to benefit from these new approaches is also emerging from these trials. It is anticipated that by aligning patient disease characteristics to biological therapeutic effects, "matches" will occur

and lead to more effective disease control. How will this information be eventually translated into individual patient care (Figure 6)? When patients with asthma that is not well controlled are evaluated for the next step in treatment, the detailed assessment will establish the presence of asthma, its severity, and phenotypic features, including available biomarkers, and then match these features to the effect of the various biologics available. It is proposed that this approach will lead to a personalizing of treatment and result in greater precision of care and effectiveness. As this comes to pass, a new era of asthma treatment will follow and have greater precision.

These are exciting times as new therapeutics emerge along with a greater mapping of mechanistic characteristics of an individual patient's asthma, their endotype. As these fields of knowledge merge, the effectiveness and precision of treatment will follow, which provides patients and physicians with a greater promise for disease control and eventual march to a cure.

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