

Biologics and biomarkers for asthma, urticaria, and nasal polyposis



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Activity Objectives:

1. To understand the immunopathologic mechanisms underlying different phenotypes of allergic disorders.
2. To describe the mechanism of action of the biologic agents available for treatment of the allergic diseases of asthma, nasal polyposis, and urticaria.
3. To distinguish the biologic agent associated with clinical improvement in different allergic phenotypes with distinct underlying mechanisms.

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Many patients with allergic disorders continue to have uncontrolled symptoms despite new and better pharmacologic options. Novel biologic agents that target specific and critical pathophysiologic pathways have been developed to better manage these patients. The utility of biologic agents for the management of allergic diseases has been facilitated by recent advances in better characterizing patients, including identification of relevant biomarkers that predict clinical responsiveness. This has led to the ability to phenotype and endotype patients, allowing for a more rational approach to picking a specific biologic agent for a specific patient. In this review I focus on point-of-care biomarkers that enhance the

usefulness of biologics to manage uncontrolled asthma, urticaria, and nasal polyposis. I discuss biologic agents already approved for the management of allergic and respiratory disorders and biologics currently in development or recently abandoned because of a lack of efficacy or intolerable side effects. The successes and failures of biologics in clinical trials have facilitated our ability to better understand which molecules and pathways are most important in the pathogenesis of allergic diseases and in the development of symptoms and impairment in individual patients. (*J Allergy Clin Immunol* 2017;139:1411-21.)

Key words: Biologics, asthma, urticaria, nasal polyps, mAbs, cytokines, IgE

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Despite recent advances in the pharmacologic management of allergic and respiratory disorders, many patients continue to have uncontrolled symptoms. Advances in the understanding of key pathophysiologic mechanisms involved in allergic and respiratory disorders have led to the possibility of more targeted therapy or “precision medicine.”¹ Precision medicine recognizes that even in patients with similar clinical presentations of a disease, the underlying pathophysiologic mechanisms can be diverse, leading to a spectrum of responses to a specific therapeutic agent

Abbreviations used

CAPS: Cryopyrin-associated periodic syndrome
 DPP-4: Dipeptidyl peptidase 4
 FDA: US Food and Drug Administration
 FENO: Fraction of exhaled nitric oxide
 IVIG: Intravenous immunoglobulin
 LS: Least square
 TSLP: Thymic stromal lymphopoietin

in patients with the same disease. For example, although corticosteroids have been remarkably effective in the management of a number of allergic disorders, including asthma, not all patients respond to them. There is a bell-shaped curve for all pharmacotherapies, indicating that distinct mechanisms of disease are likely present in nonresponders versus responders.

Researchers have relied on the development of biologic agents that target specific and critical pathways important in the pathogenesis of allergic and respiratory disorders to address the lack of responsiveness to a number of pharmacologic agents. A biologic agent refers to an antibody, vaccine, or interleukin used to treat disease, and in this article I will focus on the utility of mAbs as biologics for the management of allergic and respiratory diseases. However, as with traditional pharmacotherapies, not all patients respond to these biologic agents.^{1,2} Specific phenotypes and endotypes resulting from variations in genetic, biologic, and immunologic mechanisms coupled with distinct environmental exposures results in the heterogeneity noted in responsiveness to biologic and pharmacologic agents.

Finding which pathogenic factors are important in individual patients is a challenge in treating allergic and respiratory diseases. Broad-spectrum biologic agents that affect multiple immune pathways are problematic because of potential adverse consequences. Because of the potential for significant adverse events and the high cost of biologics, attempts at identifying biomarkers to help predict clinical responsiveness and adverse event profiles in individual patients have been critical in determining the potential utility of specific biologics for individual patients.¹⁻⁵

The characteristics of an ideal biomarker include not only the ability to identify either a clinical or treatment response but also the ease with which the biomarker can be collected and measured at the point of care. For example, although sputum eosinophils predict responsiveness to inhaled corticosteroids and many of the biologics in patients with asthma, this is a difficult-to-obtain biomarker and is not readily available to clinicians.¹⁻⁶ In this review, I will focus on biologics for the management of allergic and respiratory disorders and putative biomarkers that are easy to obtain at the point of care.

The advent of biologics for the management of allergic and respiratory diseases began many years ago but came to the forefront with the approval by the US Food and Drug Administration (FDA) of omalizumab for the treatment of chronic, persistent, moderate-to-severe perennial allergic asthma in 2003. Since then, omalizumab has been approved for the management of chronic spontaneous urticaria. In addition, many other biologics have been examined for allergic and respiratory disorders, especially asthma. The recent approval of 2 anti-IL-5 mAbs for severe asthma and the imminent approval of several other agents for asthma and other

allergic disorders have provided allergists/immunologists with unique opportunities to better manage their patients. As experts in the understanding of how these biologics work, we also have the opportunity to assess and manage adverse events associated with these agents.

In this review I will focus on the utility of biologics for several allergic and respiratory disorders, especially asthma, urticaria, and nasal polyps. Biologics in the management of atopic dermatitis will be covered elsewhere. I will review the clinical effectiveness of these agents and provide some insights into how to pick patients who might best respond therapeutically. In addition, I will review differences between similar agents in regard to dosing and secondary end point results in clinical trials that might influence individual patient preferences.

ASTHMA

Of the diseases likely to be treated with biologics by allergists and immunologists, asthma is the most prominent. There are 3 biologics currently approved by the FDA for asthma, omalizumab, mepolizumab, and reslizumab, and a number of others are in clinical development (Table 1).⁷⁻³⁵

There are 2 major inflammatory phenotypes defined for asthma: type 2–high and type 2–low asthma.¹⁻⁵ The former is typically characterized by eosinophilic inflammation and the latter by either a neutrophilic or paucigranulocytic inflammatory pattern. Most of the biologic agents developed for asthma therapy have focused on the type 2–high pattern of inflammation, probably because there are more readily available biomarkers that one can measure to identify these patients (eg, blood eosinophils). Patients with type 2–low asthma are more difficult to characterize and identify. Thus far, neutrophilic inflammation has not been detectable based on readily available point-of-care biomarkers. A recent study by Maes et al³⁶ has suggested that certain micro-RNAs in sputum might be able to accurately identify neutrophilic inflammation in the airways of patients with asthma, but most clinicians are unable to obtain satisfactory sputum samples from these patients. Paucigranulocytic inflammation is characterized by the absence of either an eosinophilic or neutrophilic inflammatory pattern. These patients likely respond best to intensive bronchodilator therapy with no specific biologics on the horizon to treat them.² Neither patients with neutrophilic nor those with paucigranulocytic asthma respond well to corticosteroids.^{1,2}

Type 2–low asthma

Biologics expected to work best in patients with the neutrophilic phenotype include agents that block key cytokines important for neutrophil chemotaxis, growth, and differentiation, including IL-8, IL-17, and IL-23.^{1,2} The neutrophil chemotactic agent IL-8 acts through the chemokine receptor CXCR2. In a small cohort of patients with severe asthma and sputum neutrophilia, a CXCR2 antagonist (SCH527123) given for 4 weeks reduced sputum neutrophil counts and mild asthma exacerbations but did not lead to significant improvements in lung functions or symptom scores.³⁷

O'Byrne et al³⁸ investigated the safety and efficacy of AZD5069, a CXCR2 antagonist, as an add-on therapy in 640 patients with uncontrolled severe asthma. Treatment with this selective CXCR2 antagonist did not reduce the frequency of severe

TABLE I. Biologics for type 2–high asthma

FDA approved therapies	Mechanism of action	Biomarkers	Effects	Indication	Route/dose/precautions	References
Omalizumab	Anti-IgE mAb Decreases expression of FcεRI	Antigen-specific IgE Better responses with higher FENO values and blood eosinophil counts >300 cells/μL	Decreased asthma exacerbations	Moderate-to-severe perennial allergic asthma in patients 6 y and older	150-375 mg of SC q2-q4 wk; frequency based on IgE and body weight Black-box warning for anaphylaxis	7-15
Mepolizumab	Anti-IL-5 mAb	Blood eosinophil count >150 cells/μL at initiation or 300 cells/μL in past year	Decreased asthma exacerbations; improvement in FEV ₁	Severe eosinophilic phenotype asthma in patients 12 y and older	100 mg of SC q4wk Consider shingles vaccine before administration	16-20
Reslizumab	Anti-IL-5 mAb	Blood eosinophil count >400 cells/μL	Decreased asthma exacerbations; improvement in FEV ₁	Severe eosinophilic phenotype asthma in patients 18 y and older	3 mg/kg administered IV q4 wk Black-box warning for anaphylaxis	21-23
In clinical trials	Mechanism of action	Biomarkers	Effects	Development phase	Likely dosing	References
Benralizumab	Anti-IL-5Rα mAb; targets eosinophils and basophils	Blood eosinophil count >300 cells/μL	Decreased asthma exacerbations; improvement in FEV ₁	Phase III in patients 12 y and older	30 mg administered SC q4 wk ×3 and then q8 wk	28,29
Tralokinumab	Anti-IL-13 mAb	Increased blood periostin and DDP-4 levels	Improvement in FEV ₁	Phase IIb trials	Not defined	32,33
Dupilumab	Anti-IL-4Rα mAb; inhibits IL-13 and IL-4	Better responses with blood eosinophil count >300 cells/μL	Decreased asthma exacerbations; improvement in FEV ₁	Phase III in patients 12 y and older	200 or 300 mg administered SC q2 wk; administered at home	7,34
AMG-157	Anti-TSLP mAb	Not defined	Reduced antigen-induced bronchoconstriction and inflammation before and after antigen challenge	II	Not defined	35
No longer in clinical development			Mechanism of action		References	
Quilizumab			Block IgE		24-27	
Ligelizumab						
Lumiliximab						
Lebrikizumab			Anti-IL-13 mAb		30,31	

IV, Intravenous; q, every; SC, subcutaneous.

exacerbations in patients with uncontrolled severe asthma. The authors concluded that these findings bring into question the role of CXCR2-mediated neutrophil recruitment in the pathobiology of exacerbations in severe refractory asthma. However, it should be noted that this study was conducted in patients not enriched for neutrophilic airway inflammation.

IL-17 can induce the production of IL-8, and IL-17 levels have been reported to be increased in the sputum of patients with severe asthma.³⁹ The IL-17 blocker brodalumab did not show clear benefits in patients with mild-to-moderate asthma, but these patients were not identified as neutrophilic.⁴⁰ Unfortunately, this mAb was associated with significant mental health issues, including risk for suicide, and is no longer being developed for asthmatic patients. IL-23 antagonists show promise in patients with psoriasis but have yet to be studied in patients with neutrophilic asthma.

Type 2–high asthma

Type 2–high asthma is characterized by eosinophilic inflammation and often associated with allergen-specific IgE levels.¹⁻⁵ Biomarkers of clinical utility to identify patients include blood and sputum eosinophil counts and either *in vitro* or *in vivo* tests for atopy. In addition, both periostin and dipeptidyl peptidase-4 (DPP-4) have proved useful, especially in identifying patients who respond to IL-13–blocking agents.^{1,2} Fraction of exhaled nitric oxide (FENO) is also a biomarker used to identify patients in this category.¹⁻⁵

Below are some biologics used to treat type 2–high asthma (Fig 1). It should be noted that with the exception of omalizumab, these agents have been studied primarily in patients not classified according to the presence or absence of allergies. Rather, specific biomarkers, such as blood eosinophils, have been shown to be the

TABLE II. Biologics for nasal polyps

mAb	Target	Effects	Development phase	References
Omalizumab	IgE	Decreased polyps, sinus opacification, symptoms	PoC	13
Mepolizumab	IL-5	Decreased polyps and need for surgery	II	47,48
Reslizumab	IL-5	Decreased polyps	PoC	48
Dupilumab	IL-4 and IL-13	Decreased polyps, sinus opacification, symptoms	III	49,50

PoC, Proof of concept.

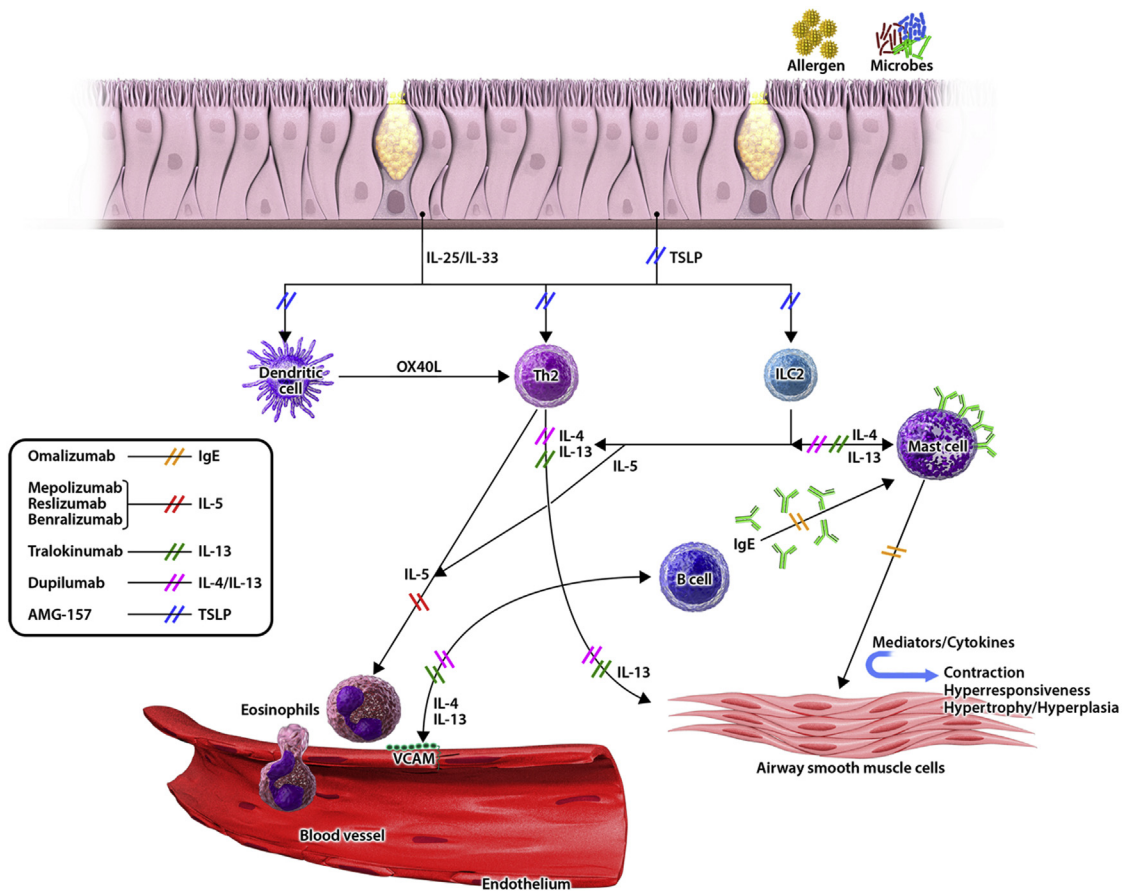


FIG 1. Therapeutic targets for type 2-high inflammation in asthmatic patients. The figure shows cytokines and mediators released from epithelial and inflammatory cells acting on other cells important in the pathogenesis of asthma. The box shows biologics and their targets, which are integrated into the figure by colored cross hatches.

best predictors of efficacy. Indeed, early studies with IL-5–blocking agents did not show significant efficacy in the absence of blood eosinophilia, even in the presence of antigen-specific IgE.

IgE-blocking strategies. There have been 4 mAb strategies that target IgE (anti-M1 prime, anti-CD23, anti-IL-4/IL-13, and anti-IgE) that have been studied for the therapy of asthma.

The anti-M1 prime mAb quilizumab depletes IgE-expressing B cells to block IgE production. Quilizumab has been shown to block both early and late asthmatic responses by approximately 30% and reduce serum IgE levels by approximately 40%.²⁴ However, in a field trial for severe asthma, quilizumab did not show any therapeutic benefits and is no longer being developed for asthma.²⁵

Lumiliximab is an anti-CD23 mAb that cross-links CD23 on B cells, resulting in decreased IgE production. Lumiliximab

decreased serum IgE levels by about 40%. However, lumiliximab failed in field trials for both patients with allergic asthma and those with rhinitis and is no longer in clinical development for asthma or rhinitis.²⁶

Dupilumab blocks the effects of both IL-4 and IL-13 by binding to the common α -chain of the IL-4 receptor (Fig 2). Dupilumab has been shown to decrease IgE levels by approximately 40%.⁷ In contrast to the previously discussed IgE-blocking strategies, which also decrease IgE levels by a similar amount, dupilumab has good clinical effects in patients with asthma, atopic dermatitis, and nasal polyposis, which will be discussed later in this review. It is likely that these positive clinical effects are related to blocking pathophysiologic events mediated by IL-4 and IL-13 independent of IgE production. Indeed, the effects of the anti-IgE mAb omalizumab appeared dependent on the degree to which

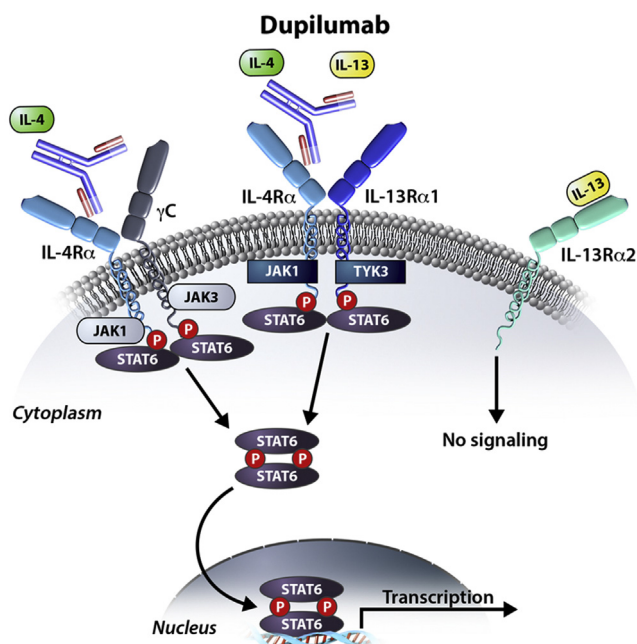


FIG 2. Mechanism of action of dupilumab. Dupilumab binds to the IL-4 α chain prohibiting either IL-4 or IL-13 from binding and subsequent signaling through the STAT6 pathway.

IgE levels were decreased, with better clinical effects at dosages that reduced IgE levels by 90% or more.⁸ This suggests that substantial reductions in IgE levels are necessary to bring about a clinical response.

Omalizumab was approved in 2003 by the FDA for patients with moderate-to-persistent allergic asthma that was not well controlled on current therapy. Until relatively recently, biomarkers to predict the responsiveness of patients to omalizumab were not identified. Hanania et al⁹ analyzed data from the EXTRA study and found that omalizumab was more efficacious in patients with higher levels of blood periostin, blood eosinophil counts, or FENO values. Busse et al¹⁰ confirmed that patients with eosinophil counts of greater than 300 cells/ μ L responded better to omalizumab, with up to a 60% decrease in asthma exacerbations. Efficacy studies of other biologics to treat type 2–high asthma have included highly enriched patient populations.

Using a similar approach, we examined data from 2 phase III clinical trials of omalizumab in patients with allergic asthma.¹¹ Differences in rates of asthma exacerbations between the omalizumab ($n = 542$) or placebo ($n = 529$) groups during the 16-week inhaled corticosteroid dose-stable phase were evaluated with respect to baseline blood eosinophil counts and baseline markers of asthma severity. The rate of exacerbations requiring 3 or more days of systemic corticosteroid treatment was 0.066 and 0.147 with omalizumab versus placebo, representing a relative rate reduction in omalizumab-treated patients of 55% (95% CI, 32% to 70%; $P = .002$). Mean exacerbation rate reductions associated with omalizumab by baseline blood eosinophil strata were as follows: 200/ μ L or greater, 52% (95% CI, 20.3% to 71.5%; $P = .005$); 300/ μ L or greater, 65% (95% CI, 30.6% to 82.0%; $P = .003$); and 400/ μ L or greater, 72% (95% CI, 34.9% to 87.6%; $P = .003$). In patients with more severe asthma (emergency asthma treatment or asthma hospitalization in the prior

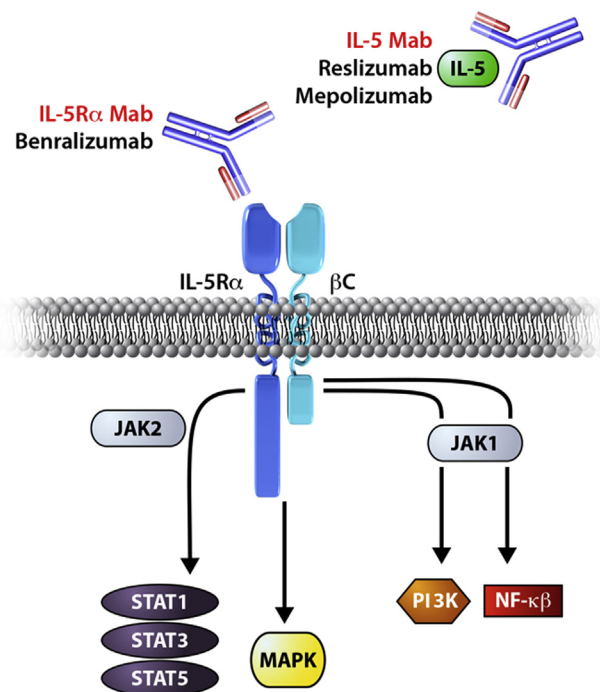


FIG 3. Anti-IL-5 strategies. Reslizumab and mepolizumab bind to IL-5 whereas benralizumab binds to the IL-5 α chain preventing IL-5 from binding and mediating antibody-dependent cell mediated cytotoxicity of cells bearing this receptor.

year, FEV₁ <65% of predicted value, use of beclomethasone ≥ 600 μ g/d, and long-acting β -agonist use), this rate reduction was more pronounced. This reduction in exacerbation rates compares favorably with those found with other biologics aimed at type 2–high asthma in similarly selected patients. However, it should be noted that even in an enriched patient population, omalizumab often does not show clinically meaningful improvements in lung functions in contrast to the other biologics discussed below.

In case reports and small case series, omalizumab has also been shown to be effective in patients with nonallergic asthma.^{12–15} It is not clear whether the patients had high blood eosinophil counts in these reports.

Another anti-IgE mAb, ligelizumab, with approximately 50-fold greater affinity for IgE has been shown to inhibit allergen-induced skin test responses and reduce IgE levels to a greater degree than omalizumab.²⁷ However, in a field study of asthmatic patients, it did not have any better effects than omalizumab, and further development for asthma has been discontinued (<https://www.novartis.com/our-work/research-development/clinical-pipeline>).

IL-5–blocking strategies. High eosinophil counts can persist in patients with severe asthma receiving multiple controller medications, including corticosteroids. Furthermore, patients with persistent asthma and high blood eosinophil counts have more frequent exacerbations.^{41,42} IL-5 is an important cytokine in eosinophil biology, promoting eosinophil differentiation, chemotaxis, activation, and survival.⁴³

Thus blocking the effects of IL-5 should prove useful in asthmatic patients with eosinophilic inflammation. Three biologics using 2 different approaches have been studied in patients with severe asthma and eosinophilic inflammation (Fig 3).

Mepolizumab and reslizumab are anti-IL-5 mAbs approved by the FDA for the treatment of patients with severe persistent asthma with an eosinophilic phenotype. Benralizumab binds to the α -chain of the IL-5 receptor present on both eosinophils and basophils, resulting in depletion of these key inflammatory cells through antibody-dependent cell-mediated cytotoxicity. All 3 agents result in decreased airway and blood eosinophil counts.

In a pivotal phase 3 study subcutaneously administered mepolizumab reduced asthma exacerbations by 53% (1.74 vs 0.83, $P < .001$) and improved FEV₁ by about 100 mL.¹⁶ Patients also reported better asthma quality-of-life scores and decreased emergency department visits and hospitalizations. Patients in this study were 12 years of age or older, had a history of asthma exacerbations in the previous year, and had a blood eosinophil count of 150 cells/ μ L at screening or greater than 300 cells/ μ L in the previous year. In a planned subanalysis of 177 patients with blood eosinophil counts of greater than 500 cells/ μ L, 100 μ g of mepolizumab administered subcutaneously monthly resulted in an 80% reduction in asthma exacerbations and improvements in FEV₁ before and after bronchodilator at 132 and 222 mL, respectively. These and other data suggest that patients with higher blood eosinophil counts are more likely to have better benefit when treated with mepolizumab.^{16,17}

Mepolizumab has also been shown to have corticosteroid-sparing effects, reducing the requirements for corticosteroid dose by greater than 50% with a concomitant reduction in asthma exacerbations and improved symptom scores.^{18,19}

It is unclear how long treatment with mepolizumab (or other biologics) should continue once the patients' symptoms are under better control. There is no evidence of treatment-induced asthma remission, and 1 report suggested that cessation of mepolizumab resulted in recurrence of symptoms and eosinophils to pretreatment levels.²⁰ Mepolizumab is not approved for any other eosinophilic condition.

Reslizumab is also approved for severe asthma with an eosinophilic phenotype, but unlike mepolizumab, the approved formulation is administered intravenously on a monthly weight-based schedule (3 mg/kg). Pivotal year-long studies with reslizumab have typically enrolled patients with blood eosinophil counts of greater than 400 cells/ μ L.²¹ In 2 phase III studies patients receiving reslizumab had a significant reduction in the frequency of asthma exacerbations (study 1: rate ratio, 0.50 [95% CI, 0.37-0.67]; study 2: rate ratio, 0.41 [95% CI, 0.28-0.59]; both $P < .0001$) and improved FEV₁, asthma control parameters, and quality-of-life scores compared with those receiving placebo. Shorter-term (16 week) studies by Corren et al²² and Bjermer et al²³ showed that reslizumab increased FEV₁ by greater than 200 mL and improved quality-of-life measures in patients with severe asthma. It is not clear whether the greater improvements in FEV₁ noted with reslizumab are due to the intravenous administration, weight-based dosing, or both. Studies are ongoing to develop an approved fixed-dose subcutaneous formulation of reslizumab. Results of these studies should help inform whether the effects on FEV₁ are related to intrinsic properties of reslizumab or how the drug is administered. Reslizumab is not approved for other eosinophilic conditions.

Two similar benralizumab year-long phase 3 studies have recently been completed and reported.^{28,29} Two different dosing regimens were studied: 30 mg administered subcutaneously every 4 weeks or 30 mg administered subcutaneously every 4 weeks for 3 doses followed by 30 mg every 8 weeks. Patients were stratified

(2:1) by baseline blood eosinophil counts (ie, >300 or <300 cells/ μ L, respectively). Both dosing regimens were shown to be effective and relatively equivalent. Benralizumab's effects were greater in patients with blood eosinophil counts of greater than 300 cells/ μ L, reducing exacerbations by 45% to 51% in one study and 28% to 36% in the other. In both studies benralizumab improved FEV₁ in patients with higher blood eosinophil counts by 106 to 159 mL, with no differences between the 2 dosing regimens. Benralizumab also improved symptom scores and quality-of-life measures. Positive treatment effects were evident at 4 weeks.

Relapse at 12 weeks after an acute asthma exacerbation is 40% to 50%, despite systemic corticosteroids. Thus there is a need to reduce the recurrence of asthma exacerbations and therefore improve patient outcomes and lower health care expenditures. In patients treated according to guidelines in the emergency department for asthma exacerbations, a single intravenous benralizumab dose of 0.3 to 1 mg/kg reduced overall exacerbation rates by 49% (3.59 vs 1.82, $P = .01$) and exacerbations resulting in hospitalization by 60% (1.62 vs 0.65, $P = .02$). Although the primary end point of the study was assessed at 84 days, beneficial effects were noted for at least 180 days after a single benralizumab administration.⁴⁴ These data imply a potential novel therapeutic role for biologics, such as benralizumab, in reducing recurrent asthma exacerbations after an initial emergency department visit.

IL-13-blocking strategies. Because of the putatively important role of IL-13 in asthma pathogenesis, various strategies have been developed to block the effects of IL-13 for the management of asthma. Two mAbs against IL-13 (tralokinumab and lebrikizumab) have been assessed in clinical trials. IL-13 stimulates bronchial epithelial cells to produce periostin and DPP-4. Both of these molecules have been used as biomarkers to predict responses to tralokinumab and lebrikizumab.^{1,2}

An initial study by Corren et al³⁰ showed that lebrikizumab improved FEV₁ in asthmatic patients whose symptoms were inadequately controlled with inhaled corticosteroids. Lebrikizumab's effects on FEV₁ were greater in patients with higher periostin values (8.2% vs 1.6%, respectively). Duplicate phase 3 trials with lebrikizumab in patients with severe asthma were done; one study showed positive results, although the second did not, even with the use of biomarkers to enrich patient populations.³¹ The development of lebrikizumab for asthma has been stopped.

Tralokinumab has also had variable results in clinical trials. An initial phase 2 trial with various doses of tralokinumab administered subcutaneously biweekly did not demonstrate improvements in asthma exacerbations or symptoms but did show improvements in FEV₁.³² A second study conducted by Brightling et al³³ showed that tralokinumab dosed biweekly for 52 weeks did not improve asthma exacerbation rates compared with placebo in the overall population but did so in patients who had higher periostin or DPP-4 levels.

Dupilumab has a theoretical advantage over lebrikizumab and tralokinumab by blocking the effects of both IL-4 and IL-13. In a study by Wenzel et al,⁷ patients with inadequately controlled asthma and either blood or sputum eosinophilia who were administered dupilumab subcutaneously on a weekly schedule had decreased asthma exacerbations and improvement in many secondary end points, including FEV₁. A second study by Wenzel et al³⁴ showed that a biweekly dose of dupilumab primarily administered at home resulted in reductions in asthma

TABLE III. Biologics for urticaria

Biologics	Target	Diseases studied	References
Omalizumab	IgE	CSU (FDA approved) Physical urticaria Urticarial vasculitis	15,53-63
Quilizumab	IgE	CSU	64
Etanercept	TNF- α	CSU	65-67
Adalimumab		Physical urticaria	
Infliximab		Urticarial vasculitis	
Rituximab	CD20	CSU Physical urticaria Urticarial vasculitis	65
Anakinra	IL-1	CAPS	68-73
Canakinumab		Schnitzler syndrome	
Rilonacept		CSU Urticarial vasculitis	
IVIG	ND	CSU Physical urticaria	65,74

CSU, Chronic spontaneous urticaria; ND, not determined.

exacerbations and improvements in pulmonary function values regardless of pretreatment blood eosinophil levels, although results were better in patients with blood eosinophil counts of greater than 300 cells/ μ L. Adjusted annualized severe exacerbation event rate estimates were 0.897 (95% CI, 0.619-1.300) in the placebo group and 0.265 (95% CI, 0.157-0.445) in the biweekly 300-mg dose in the overall patient population and 1.044 (95% CI, 0.572-1.904) and 0.201 (95% CI, 0.078-0.517), respectively, in patients with blood eosinophil counts of greater than 300 cells/ μ L. If these results are replicated, dupilumab could prove to be a good choice for patients with lower blood eosinophil counts and uncontrolled asthma. Whether it works in patients with type 2–low asthma remains to be determined.

Strategies against epithelial cell alarmins. Airway epithelium–derived cytokines, such as IL-25, IL-33, and thymic stromal lymphopoietin (TSLP), are collectively known as epithelial alarmins. IL-33 and TSLP promote type 2–high inflammation, leading to production of type 2 innate lymphoid cells, which release cytokines important for eosinophilic inflammation. Furthermore, it is postulated that these cytokines might inhibit the generation of regulatory T cells.

Thus far, only an mAb to TSLP, AMG 157, is in clinical development for asthma. Treatment with AMG 157 has been reported to reduce allergen-induced early and late asthmatic responses, blood and sputum eosinophil counts, and FENO values.³⁵ Antibodies to OX40 ligand or TSLP did not alter the presence of regulatory T cells in the blood of asthmatic patients.⁴⁵ The therapeutic utility of antibodies against TSLP remains to be determined from field studies in patients with uncontrolled asthma.

NASAL POLYPOSIS

As with asthma, nasal polyposis associated with eosinophilia at the tissue level tends to be more steroid responsive. Furthermore, persistent nasal mucosal eosinophilia is associated with recurrence of nasal polyps. As reviewed by Bachert et al,⁴⁶ patients with eosinophilic or neutrophilic nasal mucosal inflammation have predominant T2 cytokine or T1 cytokine profiles, respectively. Therefore attempts at treating either of these nasal

polyposis phenotypes have focused on blocking relevant key pathogenic molecules (Table II).^{13,47-50}

Increased IgE concentrations in nasal polyp tissue and secretions resulting from local polyclonal IgE production have been found in a number of studies and associated with disease severity. As a result, proof-of-concept studies and case reports examining the effects of omalizumab on nasal polyps have been reported. In a randomized, double-blind, placebo-controlled study of 24 allergic and nonallergic patients with nasal polyps and comorbid asthma, omalizumab significantly decreased total nasal polyp scores, sinus opacification, and nasal symptoms, including anosmia.¹³ Interestingly, local nasal mucosal inflammation was not affected by omalizumab. Despite this and anecdotal case reports purporting the efficacy of omalizumab for nasal polyps, it is unclear whether there are definitive plans to gain approval of omalizumab for this indication.

Prominent nasal polyp and mucosal eosinophilia with increased tissue expression of IL-5 have prompted investigators to explore the clinical utility of IL-5–blocking strategies.^{47,48,51,52} Mepolizumab and reslizumab have been administered to patients with nasal polyps in proof-of-concept studies. Both anti-IL-5 mAbs decreased nasal polyp scores, but neither significantly improved nasal symptom scores.^{47,48} The results appeared to be better in patients with higher baseline levels of nasal IL-5 secretion. The preliminary results of a multicenter study to investigate the use of mepolizumab in reducing the need for surgery in subjects with severe bilateral nasal polyposis have been posted at <https://clinicaltrials.gov> (NCT01362244). The data suggested that mepolizumab administered for 6 months resulted in a reduced need for sinus surgery. Whether anti-IL-5 mAbs will be a viable option for the management of patients with eosinophilic nasal polyposis remains to be determined based on published phase 3 study results.

Because of the putative importance of IL-4 and IL-13 in the pathogenesis of eosinophilic polyposis, dupilumab has also been studied as a potential treatment. In a proof-of-concept study dupilumab resulted in a reduction in nasal polyps and improvement in nasal symptoms.⁴⁹ The results of a randomized, double-blind, placebo-controlled, parallel-group study of 60 adults with chronic sinusitis and nasal polyposis refractory to intranasal corticosteroids have recently been reported.⁵⁰ Subcutaneous weekly dupilumab (600-mg loading dose followed by 300 mg) or placebo plus mometasone furoate nasal spray was administered for 16 weeks. The least squares (LS) mean change in nasal polyp score by endoscopy was -0.3 (95% CI, -1.0 to 0.4) with placebo and -1.9 (95% CI, -2.5 to -1.2) with dupilumab (LS mean difference, -1.6 [95% CI, -2.4 to -0.7]; $P < .001$). The LS mean difference between the 2 groups for the Lund-Mackay sinus computed tomography total score was -8.8 (95% CI, -11.1 to -6.6 ; $P < .001$). Significant improvements were also observed for nasal symptoms, including anosmia. The authors concluded that although dupilumab showed promising results, further studies are needed to assess longer treatment duration, larger samples, and direct comparison with other medications.

URTICARIA

Chronic spontaneous urticaria is associated with intense pruritus, disfiguring hives, and poor quality of life. It is estimated that the majority of patients with chronic urticaria do not adequately respond to high-dose second-generation antihistamines.

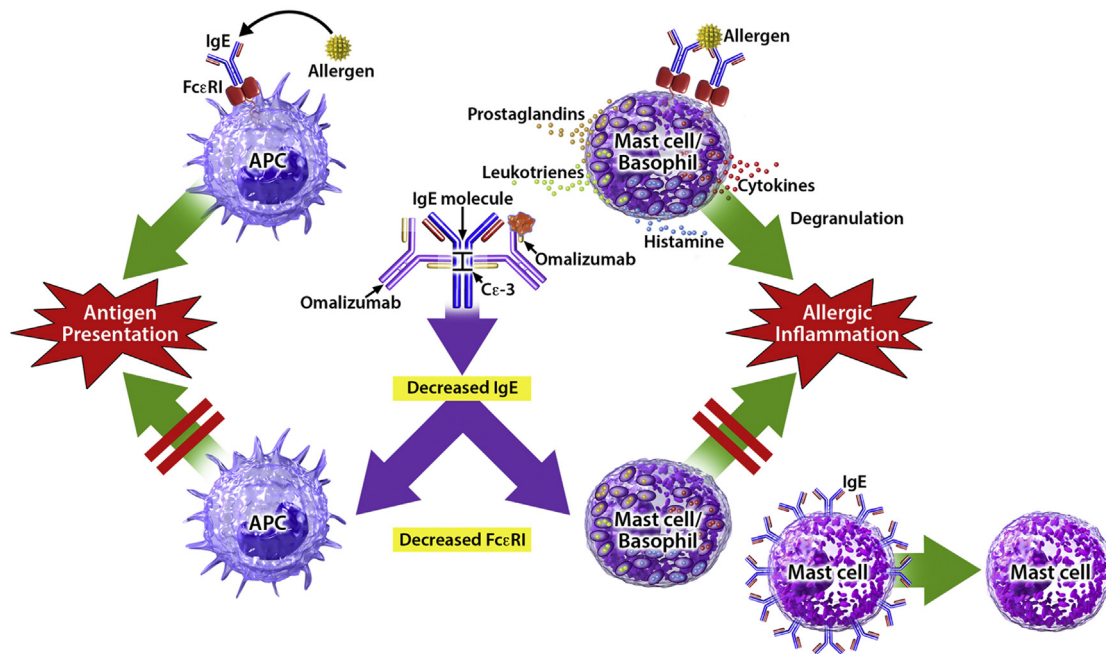


FIG 4. Mechanism of action of omalizumab. Omalizumab binds to free IgE forming small immune complexes which are cleared by the reticuloendothelial system. The reduction in IgE leads to decreased expression of the high affinity IgE receptor and decreased mediator release from mast cells and basophils and decreased antigen capture by dendritic cells.

Therefore a number of agents have been used in an attempt to control this serious disease. Among these are many biologics, especially mAbs directed at putatively important pathophysiologic mechanisms involved in the genesis of this disease (Table III).^{15,53-74} Here we will briefly discuss the therapeutic effectiveness of these mAbs, focusing on omalizumab, rituximab, TNF- α antagonists, and IL-1 antagonists for chronic urticaria and other forms of urticaria.

Omalizumab

Many patients with chronic urticaria have autoantibodies directed against the α -chain of the high-affinity IgE receptor (FcεRI) or to IgE itself, with the former more specific for chronic spontaneous urticaria. Because omalizumab markedly decreases circulating IgE levels and results in the consequent reduction in expression of FcεRI (Fig 4), omalizumab was proposed as a therapy for patients with chronic urticaria and autoantibodies.⁵³ In proof-of-concept and phase 2 studies, the benefits of omalizumab were demonstrated in patients with and without autoantibodies.⁵⁴⁻⁵⁶ Subsequently, phase 3 studies showed that patients refractory to high-dose antihistamines alone or in combination with other medications had significant improvements in urticaria, including reductions in pruritus and hives and improvements in quality-of-life measures.⁵⁷⁻⁵⁹ The effects of omalizumab were shown to be dose dependent, and at the highest dose studied, 300 mg administered subcutaneously on a monthly basis, complete resolution of urticarial symptoms was found in a significant proportion of patients. A review of the effects of omalizumab in patients with chronic urticaria showed that it was effective regardless of background therapy or patient demographics.⁶⁰

The efficacy and safety of omalizumab for chronic urticaria resulted in approval by both US and European regulatory agencies of omalizumab for the management of antihistamine-resistant chronic urticaria. Omalizumab is now added to urticaria therapy as a fourth step in the US guidelines after failure of antihistamines at both standard and high doses, addition of an H₂-antihistamine and leukotriene antagonists, and failure of a high-potency antihistamine, such as doxepin or hydroxyzine.⁶¹ However, the European guidelines recommend omalizumab as the third step for chronic urticaria management after the failure of nonsedating antihistamines at standard and high doses.⁶² A recent meta-analysis has confirmed the efficacy of omalizumab for chronic spontaneous urticaria, as well as angioedema-related symptoms, in these patients.⁶³

Omalizumab has also been used for a variety of other forms of urticaria, including urticarial vasculitis and a number of physical urticarias. Although most of the data supporting omalizumab's effectiveness in patients with other urticarial disorders are from anecdotal case reports or small case series, positive results have been found for cholinergic, cold, heat, aquagenic, delayed pressure, solar, and dermatographic urticaria.¹⁵

Quilizumab

Based on the positive results for omalizumab, it is thought that IgE is an important factor in the pathogenesis of chronic spontaneous urticaria. Therefore investigators have examined the effects of quilizumab to treat patients with chronic urticaria.⁶⁴ In a proof-of-concept study quilizumab reduced median serum IgE levels by approximately 30% in patients but did not cause clinically meaningful improvements in urticaria or

TABLE IV. Future needs for optimization of biologics for allergic diseases

Inexpensive and easily obtainable point-of-care biomarkers
Biomarkers for type 2–low asthma
Safe and effective biologics for type 2–low asthma
Phenotype/endotype (biomarker)–driven, biologic-specific therapies (precise patient therapy)
Biologics that induce true immunomodulation: prevent/alter disease course
Biologics with favorable risk/benefit ratio
Biologics with convenient dosing
Affordable/cost-effective biologics
Biologics that prevent recurrent emergency department visits

pruritus symptom scores. The authors concluded that ongoing IgE switching and stimulation of B-cell memory might not be key disease drivers in the pathogenesis of chronic urticaria, and additional studies will be required to fully understand the etiology of this disease and the potential role of other IgE-blocking strategies.

TNF- α antagonists

Etanercept, adalimumab, and infliximab have all been tried as therapeutic options for various types of urticarial disorders.⁶⁵ The rationale for the utility of these agents comes from studies suggesting that there is an upregulation of TNF- α expression in the skin of patients with chronic urticaria.^{75,76} Promising results have been demonstrated in patients with a variety of physical urticarias, urticarial vasculitis, and chronic urticaria, but the data are limited mostly to case reports and small uncontrolled studies.^{65,66} In a retrospective study of 118 patients with chronic urticaria, 60% obtained complete or almost complete resolution of urticaria and angioedema after onset of therapy with either adalimumab or etanercept, and another 15% of patients experienced partial response to therapy. Interestingly, the authors stated that some of their patients were previously unresponsive to omalizumab.⁶⁷

Rituximab

Rituximab is an anti-CD20 mAb that causes antibody-dependent cell-mediated cytotoxicity of immature, mature, and memory B cells that express CD20. Rituximab is postulated to have a role in the management of urticaria by targeting the B cells that produce IgE and autoantibodies against Fc ϵ RI.⁶⁵ Some promising results have been demonstrated in case reports of patients with chronic urticaria, urticarial vasculitis, and various physical urticarias. However, there is a lack of double-blind, randomized, placebo-controlled trials supporting the effects of rituximab for the management of antihistamine-resistant chronic urticaria.⁶⁵

Intravenous immunoglobulin

Because of the postulated role of autoimmunity and autoantibodies, especially to Fc ϵ RI, intravenous immunoglobulin (IVIG) has been evaluated for the management of chronic urticaria and various physical urticarias. There have been a number of small case series showing that either pulse or monthly doses of IVIG can improve or lead to complete

remissions of chronic urticaria.⁶⁵ These benefits have been noted in patients with and without demonstrated autoantibodies. A study by Pereira et al⁷⁴ showed that monthly infusions of low-dose IVIG (0.15 g/kg) resulted in positive results in 90% of patients, with almost two thirds having complete remission after 6 to 51 months of therapy. Because of the success of IVIG in patients with chronic urticaria, it has also been examined in delayed pressure and solar urticaria with variable results.

IL-1 antagonists

Cryopyrin-associated periodic syndromes (CAPSs), which are caused by autosomal dominant mutations of the nucleotide-binding domain, leucine-rich family, pyrin domain containing 3 gene (*NLRP3*), are associated with altered synthesis of cryopyrin and the subsequent overproduction of IL-1 β . CAPSs represent a spectrum of autoinflammatory syndromes, including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease, which are often associated with urticaria.⁶⁸⁻⁷⁰ Because of the important role of IL-1 β , therapies directed against this cytokine have been evaluated and approved by the FDA for the treatment of CAPSs, including anakinra, a recombinant human IL-1 receptor α antagonist; canakinumab, a humanized anti-IL-1 β mAb; and rilonacept, which blocks IL-1 β signaling by acting as a soluble decoy receptor. IL-1 is also thought to play a critical role in Schnitzler syndrome manifested by urticaria, fever, myalgias, and lymphadenopathy. Anakinra and canakinumab have been reported to induce significant improvements in patients with Schnitzler syndrome.^{71,72} The role of IL-1 and IL-1 antagonists in patients with chronic spontaneous urticaria remains to be determined. A clinical trial of canakinumab for chronic urticaria (<https://clinicaltrials.gov>, NCT01635127) is ongoing. IL-1 antagonists have also been used for the management of urticarial vasculitis.⁷³

SUMMARY/BIOLOGICS IN PATIENTS WITH OTHER ALLERGIC DISORDERS

Because of the putatively important role of cytokines in patients with a number of allergic and respiratory disorders, trials of biologics have been used to examine the therapeutic benefits of cytokine blockers and better define the pathogenesis of many of these disorders. Examples of clinical studies involving biologics other than those already discussed include antagonists of IL-5 for eosinophilic disorders, including idiopathic hypereosinophilic syndrome, eosinophilic chronic obstructive pulmonary disease, and eosinophilic esophagitis; dupilumab for atopic dermatitis; and omalizumab for rhinitis and anaphylaxis and as an adjuvant to prevent systemic reactions from immunotherapy and improve its clinical effectiveness. Thus far, biologics aimed at inhibiting type 2 inflammatory pathways and eosinophilia have proved effective and relatively safe (Fig 1). In contrast to allergen immunotherapy, the biologics discussed have not been shown to prevent the development of new sensitizations and diseases, such as asthma, and/or induce disease remission, features of immune tolerance induction (Table IV). Nonetheless, our abilities to treat allergic and immunologic disorders have

improved considerably with the advent of the development of mAbs and other biologics.

What do we know?

- IgE plays an important role in the pathogenesis of asthma, urticaria, and nasal polyps (in some patients), providing a rationale for the use of omalizumab.
- Blocking IL-5 is effective in treating patients with asthma and some patients with nasal polyps.
- Strategies aimed at blocking both IL-4 and IL-13 are important in treating multiple allergic and respiratory diseases, including asthma, atopic dermatitis, and nasal polyps.
- IL-1 antagonists are important treatments for CAPSs.

What is still unknown?

- How to diagnose and optimally treat type 2–low asthma
- What biomarkers can be used to predict optimal responses of individual patients with type 2–high asthma to specific type 2–high asthma–targeted biologics
- How to induce true immunomodulation of allergic diseases
- Whether blocking IL-13 alone will be an effective strategy for asthma management
- Whether biologics other than omalizumab will prove effective in patients with chronic spontaneous urticaria

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