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Review

Strategies for choosing a biologic for your patient with allergy or asthma

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Key Messages

- Approved biologics for the treatment of asthma include omalizumab, mepolizumab, reslizumab, benralizumab, and dupilumab. Possible future therapies include tezepelumab and astegolimab.
- The only currently approved biologic for urticaria is omalizumab. Possible future therapies include ligelizumab, dupilumab, lirentelimab, mepolizumab, benralizumab, tezepelumab, and Celldex.
- Approved biologics for nasal polyps include dupilumab, omalizumab, and mepolizumab. Benralizumab is a possible future therapy.
- The only currently approved biologic for atopic dermatitis is dupilumab. Possible future therapies include interleukin (IL)-13 blockers, tezepelumab, fezakinumab, and nemolizumab.
- There are currently no biologics which the Food and Drug Administration approved for the treatment of food allergy. Possible future therapies include omalizumab, ligelizumab, dupilumab, and etokimab.
- There are currently no biologics approved by the Food and Drug Administration for the treatment of eosinophilic esophagitis. Possible future therapies include dupilumab, lirentelimab, mepolizumab, reslizumab, benralizumab, IL-13–blocking agents, anti–IL-15 agents, and anti–tumor necrosis factor alpha agents.

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ABSTRACT

Objective: To summarize the therapeutic effects and safety of biologics either approved or in clinical development for asthma, chronic obstructive pulmonary disease, urticaria, nasal polyps, atopic dermatitis, and eosinophilic esophagitis. This review attempts to provide some guidance when choosing among agents.
Data Sources: Recently published articles obtained through PubMed database searches including research articles, review articles, and case reports.
Study Selections: PubMed database searches were conducted using the following keywords: biologics, asthma, COPD, urticaria, atopic dermatitis, food allergy, nasal polyps, and eosinophilic esophagitis.
Results: The approval of omalizumab by the Food and Drug Administration in 2003 for patients with asthma paved the way for the development of multiple biologics for a variety of respiratory and allergic diseases. Agents approved by the Food and Drug Administration include mepolizumab, reslizumab, benralizumab, and dupilumab, and several more are in the late stages of clinical development. Owing to the overlap in the pathogenesis of respiratory and allergic diseases, many of these biologics target multiple respiratory and allergic diseases simultaneously.

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Conclusion: The numerous biologic options have made the selection of the best biologic for each patient a potential conundrum for clinicians. Adequate point of care biomarkers to facilitate personalized medical therapy are generally lacking. Furthermore, although clinically effective and generally safe, none of the biologics discussed in this review have induced long-standing disease remission. Nevertheless, these agents have given us the opportunity to treat the most severe patients and to better understand the biology of respiratory and allergic diseases. As knowledgeable physicians, we should embrace and be educated on these novel therapies and the pathways they target.

Introduction

One of the most exciting and rapidly growing areas of allergy and immunology is the development of targeted biologic therapies for allergic and respiratory diseases. Just within the 3 years that our previous review article in the *Annals* regarding this subject was published,[1] new agents and new indications for existing agents have exploded onto the scene (Fig 1). Now more than ever, figuring out which biologic to choose can be a tricky process. The goal of this review is to build on the previous article and to provide further clinical situations in which one biologic may be preferred over another.

Asthma

Severe asthma is defined as asthma that is treated with a high-dose inhaled corticosteroid and an additional controller medication or systemic corticosteroids with or without other controllers,[2] or remains uncontrolled despite these therapies. Severe asthma endotypes describe the underlying pathogenesis and include type 2 (T2)-high, T2-low, or a mix of both. Type 2–high suggests the presence of T_H2 CD4-positive lymphocytes that characteristically secrete interleukin (IL) 4, 5, 9, and 13.[3] These cytokines cause airway inflammation and remodeling in the epithelium and subepithelial matrix.[3] Immunoglobulin E (IgE)-mediated hypersensitivity reactions initiate or propagate the secretion of these cytokines in a subset of T2-high asthma. Asthma phenotypes are the clinical manifestations that result from endotype-environment interactions.

Phenotype-targeted therapies may improve asthma outcomes, considering that many patients remain symptomatic with controller therapy that does not distinguish among asthma phenotypes. Variation in clinical response to therapy can be linked to genetic, pharmacologic, physiological, and immunologic differences.[4] In response, biologic monoclonal antibody medications were developed to target specific pathways implicated in asthma biology and have considerably reduced the morbidity associated with severe asthma. The US Food and Drug Administration (FDA) currently has approved 5 biologics for the treatment of patients with severe asthma. The pivotal studies for the 4 most recently approved biologics enrolled patients with severe T2 asthma, even if they varied in their eligibility criteria and definitions for eosinophilic disease. For example, T2-high disease has been defined with sputum eosinophil levels greater than or equal to 1%, blood eosinophil levels greater than or equal to 150 cells/μL, or fractional exhaled nitric oxide (FeNO) levels greater than or equal to 20 parts per billion, but other thresholds have been proposed in this contentious debate. Patients with allergic asthma have worsening symptoms when exposed to aeroallergens, and their serum IgE level usually exceeds 30 IU/mL.

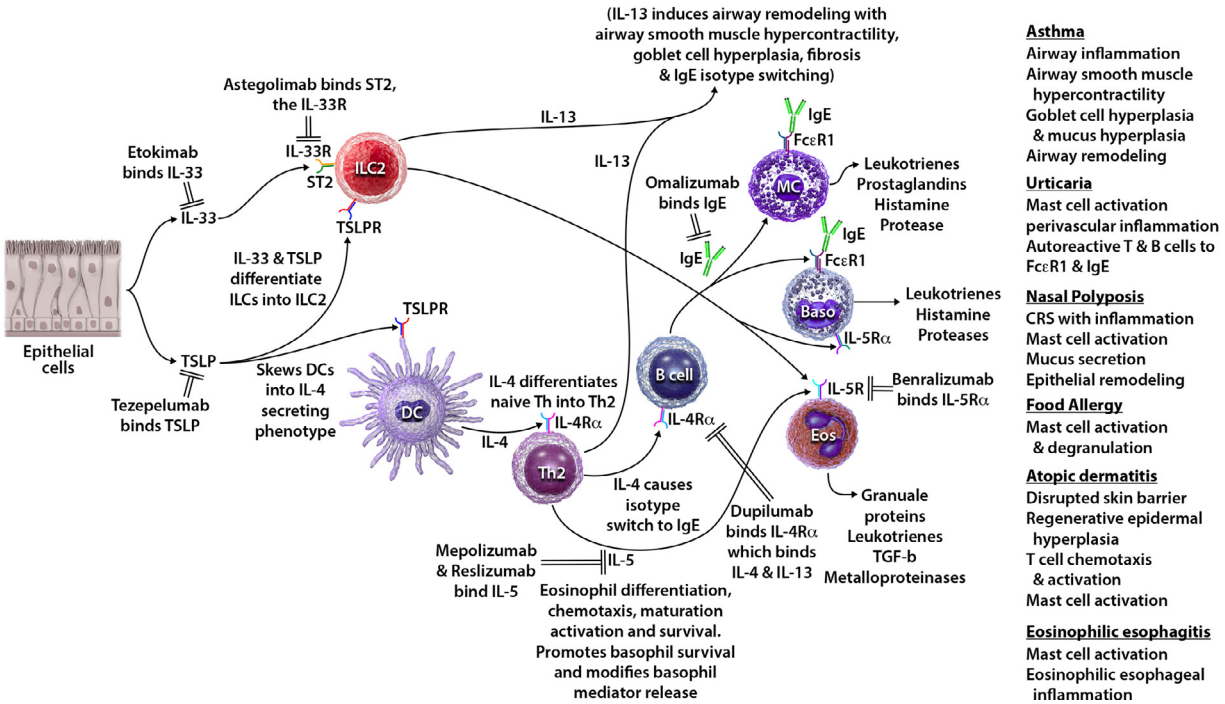

Figure 1. Cellular and molecular targets for biologics used in the treatment of allergic diseases. Baso, basophils; CRS, chronic rhinosinusitis; DC, dendritic cells; Eos, eosinophils; FcER1, high-affinity IgE receptor; IgE, immunoglobulin E; IL, interleukin; ILC2, type 2 innate lymphoid cell; MC, mast cells; R, receptor; ST2, soluble interleukin 1 receptor-like 1, which is the receptor for IL33; TGF-beta, transforming growth factor-beta; T_H2, T helper 2; TSLP, thymic stromal lymphopoietin.

Omalizumab

The first biologic approved by the FDA for use in patients with moderate-to-severe persistent allergic asthma was omalizumab (Xolair, Genentech, South San Francisco, California) in June 2003. Omalizumab is a monoclonal antibody that targets IgE, which prevents its binding to the high-affinity IgE receptor (FcεR1) on basophils, mast cells, and dendritic cells. The lack of engagement by IgE causes down-regulation of FcεR1 on these cells, with important implications in asthma biology such as decreased pro-asthmatic mediator release by mast cells and basophils and increased interferon production by plasmacytoid dendritic cells.[5] In a phase III trial of patients with severe allergic asthma, the addition of omalizumab reduced the average number of asthma exacerbations by 48% compared with placebo.[6] In the subset of patients with peripheral eosinophil levels of at least 400/μL, reductions in asthma exacerbations were reported to be 74%.[7] In contrast with eosinophil counts, neither baseline IgE levels nor the number and type of allergen sensitizations predict the likelihood of response.[8] In an open-label pragmatic trial, omalizumab led to a 39% reduction in daily oral corticosteroid (OCS) use more than 52 weeks, and improvement in quality-of-life questionnaire scores when compared with responses 1 year before.[8] In a real-world study of omalizumab in patients 12 years and older with allergic asthma, half of the 85% of patients with uncontrolled symptoms at baseline using the asthma control test achieved good asthma control (asthma control test score, ≥20) after 12 months of using omalizumab.[9] Comorbid conditions that favor the use of omalizumab include chronic rhinosinusitis with nasal polyposis (CRSwNP), chronic urticaria (both FDA-approved indications), allergic rhinitis,[10] food allergies,[11] allergic bronchopulmonary aspergillosis, eosinophilic granulomatosis with polyangiitis[12] and asthma–chronic obstructive pulmonary disease (COPD) overlap syndrome (ACOS).[13] Omalizumab is approved for asthma in children 6 and above. The recommended subcutaneous dose is administered either in a health care setting or at home every 2 or 4 weeks depending on body weight and IgE levels.[14]

Mepolizumab

Omalizumab was on the market for more than 10 years before the next biologic became FDA approved. In November 2015, mepolizumab (Nucala, GalxoSmithKline, Philadelphia, Pennsylvania) was FDA-approved for use as an add-on maintenance treatment for patients with severe eosinophilic asthma aged 6 years and older.[15] Mepolizumab is an immunoglobulin G (IgG) 1 kappa monoclonal antibody that targets IL-5 and prevents it from binding to IL-5 receptors. By neutralizing IL-5, eosinophil production and survival are inhibited. In phase III clinical trials, mepolizumab reduced relative exacerbation rates by 53%[16] and in the Steroid Reduction with Mepolizumab Study (SIRIUS) trial, 63% of mepolizumab users were able to reduce their OCS use by 50% to 100%.[17] Other FDA-approved indications for mepolizumab include eosinophilic granulomatosis with polyangiitis,[15] hypereosinophilic syndromes, and CRSwNP.[18] Mepolizumab has also exhibited positive effects in allergic bronchopulmonary aspergillosis[19] and eosinophilic COPD.[20] Mepolizumab is approved for children ages 6 years and older. It is dosed as a 100-mg subcutaneous injection for patients 12 years and older and as a 40-mg subcutaneous injection for patients 6 to 11 years old every 4 weeks. It is available as an autoinjector and can be dosed at home or in the clinic.

Reslizumab

Soon after mepolizumab was FDA-approved, reslizumab (Cinqair, Teva Pharmaceutical Industries, Frazer, Pennsylvania) was approved in March 2016 for use as add-on maintenance treatment of patients with severe eosinophilic asthma who are 18 years of age and older. Reslizumab is also a monoclonal antibody that binds IL-5 but is an IgG4-kappa molecule. Reslizumab was found to reduce the frequency of asthma exacerbations at 1 year in a phase III pooled data analysis by 54% compared with placebo when blood eosinophil levels were greater than or equal to 400 cells/μL.[21] Reslizumab markedly reduces blood eosinophil counts. Elevated pretreatment blood eosinophil counts predict greater improvements in lung function and asthma control.[22] Its weight-based dosing may help patients with higher body mass index. In prednisone-dependent patients with severe asthma, weight-adjusted reslizumab was superior to fixed-dose mepolizumab in achieving asthma control.[23] Reslizumab may also be efficacious in CRSwNP.[24] It is administered as a 3 mg/kg infusion once every 4 weeks over 20 to 50 minutes.[25]

Dupilumab

Pathways other than those driven by IL-5 are also important in the pathogenesis of asthma and have led to different therapeutic options. IL-4 causes isotype switching to IgE and skews the development of naive T_H cells to T_H2 cells. IL-13 has many important roles in asthma pathogenesis including mucus production and airway hyperresponsiveness. In March of 2017, dupilumab (Dupixent, Regeneron Pharmaceuticals, Tarrytown, New York) was approved by FDA for use in patients with eosinophilic or OCS-dependent (regardless of eosinophil counts) moderate-to-severe asthma in patients ages 12 years or older.[26] In the Liberty QUEST trial dupilumab, an anti–IL-4α receptor monoclonal antibody, decreased severe asthma exacerbations in patients with moderate-to-severe asthma by 48% when compared with placebo, with a significant improvement in the levels of forced expiratory volume in 1 second by 320 mL ($P < 0.001$).[27] Patients who were corticosteroid-dependent in the phase III Liberty Asthma VENTURE trial were able to decrease their daily dose by 70% while on dupilumab compared with placebo and approximately 50% were able to completely discontinue OCS use.[28] Elevated FeNO is the most favorable predictor for responses to dupilumab independently and additively to blood eosinophils. Similar to other biologics discussed, higher baseline peripheral eosinophil counts predict better responses to dupilumab. Blood eosinophilia is an important adverse effect observed in 14% of patients on dupilumab, but this tends to resolve in many patients with time.[27,28] Although not frequently observed in asthma trials, dupilumab has been associated with the development of conjunctivitis in 9% to 28% of patients with atopic dermatitis, which is another of its FDA-approved indications. Dupilumab is also FDA-approved for the treatment of CRSwNP. It has exhibited favorable outcomes in its use for aspirin-exacerbated respiratory diseases[29] and pediatric patients with asthma younger than 12 years. In patients with eosinophilic moderate-to-severe asthma, the initial dose is a 400-mg subcutaneous injection followed by a 200-mg prefilled injection administered every 2 weeks. For patients with OCS-dependent moderate-to-severe asthma, the recommended dose is an initial 600-mg injection followed by a 300-mg prefilled injection given every 2 weeks.[26]

Benralizumab

Eight months after the approval of dupilumab in November 2017, benralizumab (Fasenra, AstraZeneca, Södertälje, Sweden) became the most recent FDA-approved biologic for asthma. It is approved for patients 12 years and older with severe eosinophilic asthma.[29] Benralizumab is a monoclonal IgG1 kappa antibody against the IL-5α receptor resulting in antibody-dependent cell-mediated cytotoxicity of cells expressing these receptors.[30] Targeting the receptor instead of the ligand itself, as in mepolizumab or reslizumab, is thought to possibly be more effective at depleting tissue-dwelling eosinophils and basophils, which also express this receptor. In its phase 3 trials,

benralizumab decreased annual asthma exacerbation rates by 45% and improved levels of prebronchodilator forced expiratory volume in 1 second by 159 mL.[31,32] Benralizumab was also found to reduce OCS use by at least 50% in two-thirds of patients.[33] It is administered as a 30-mg subcutaneous injection every 4 weeks for the first 3 doses and then once every 8 weeks.[30]

Chronic Obstructive Pulmonary Disease and Asthma–Chronic Obstructive Pulmonary Disease Overlap Syndrome

Using monoclonal antibodies targeting the IL-4, IL-5, and IL-13 and IgE signaling pathways have become an area of interest in the possible treatment of COPD and ACOS.[34,35] Patients with asthma who were included in the Prospective Observational Study to Evaluate Predictors of Clinical Effectiveness in Response to Omalizumab (PROSPERO) were not excluded for having a history of COPD or smoking. A posthoc analysis found that patients who were treated with omalizumab had similar improvements in asthma outcomes if they met the criteria for ACOS.[13] In a phase III trial of patients with COPD and eosinophil levels of at least 150/mL[4] treated with mepolizumab 100-mg subcutaneous injection every 4 weeks, there was an 18% decrease in the annual rate of moderate or severe COPD exacerbations.[20] Similar outcomes were not observed when patients with moderate to very severe COPD were studied in a phase 3 randomized clinical trial using benralizumab.[36]

Which to Choose?

Choosing the best biologic depends on the asthma phenotype, age, comorbidities, goals of therapy (eg, dupilumab for OCS reduction), triggers of exacerbations (eg, omalizumab for virus and allergen-induced exacerbations), and adverse effect profile (Table 1). Only dupilumab and omalizumab are also indicated for patients with moderate persistent asthma, whereas the rest are exclusively indicated for those with severe disease. Omalizumab and mepolizumab are approved for patients 6 years and older, benralizumab and dupilumab are approved for patients 12 years and older, and reslizumab is approved for adults 18 years and older. Omalizumab, mepolizumab, and dupilumab can simultaneously help patients with moderate-to-severe asthma and CRSwNP. Atopic dermatitis is frequently encountered in patients with asthma and dupilumab is indicated for patients 6 years and older for atopic dermatitis and 12 years and older for asthma. Insurance coverage and patient preferences of medication administration route, frequency, and location are important factors that may influence patient preference. Patient preference for achieving certain goals, such as reducing OCS dependence or improving asthma symptom control, may influence which biologic is chosen. Once a biologic is decided on, it is recommended to closely monitor symptoms and overall asthma control over a 4-to-6-month interval.[37] During follow-up, patient-related factors such as poor adherence to biologic or other asthma therapies and poorly controlled comorbidities should be optimized.[37] Persistent airway eosinophilia or T2 airway inflammation can be seen when the disease is driven by a different pathway than that targeted by the biologic chosen, or with poor adherence to therapy. When such disease-related factors are believed to contribute to a suboptimal response, it is appropriate to reassess the patient's phenotype with blood, sputum, and exhaled inflammatory markers such as blood or sputum eosinophils, FeNO, and serum total IgE (if considering a switch to omalizumab).[36] Patients who exhibit a suboptimal response may consider a longer trial of 6 to 12 months, with suboptimal response defined as less than 50% exacerbation reduction, minimal symptoms improvement, and no reduction in daily OCS or lung function improvement.[38] Patients with a suboptimal response after a review of patient, disease, and medication-related factors should be evaluated for treatment with a different biologic.[39]

The Future of Biologic Therapies and Asthma

The future of biologics in the management of asthma is promising for patients and physicians. The biologics discussed are successful at targeting various components that comprise T2 cytokines (IL-4, IL-5, IL-9, and IL-13), but for many patients with nonallergic or noneosinophilic phenotypes, there is a substantial disease burden. Thymic stromal lymphopoietin (TSLPs) is an epithelium-derived cytokine/alarmin that can activate the innate immune system in response to various viruses, allergens, and toxins that are important triggers in patients with asthma.[40,41] Tezepelumab is an IgG2 monoclonal antibody that binds to TSLP and can prevent the activation of T cells, B cells, dendritic cells, and the innate lymphoid immune cells that can secrete T2 cytokines. Tezepelumab leads to a decrease in asthma exacerbation rates in patients classified as either T2-low or T2-high.[42] In a recent phase 3 trial, the use of tezepelumab was

Table 1
Comparisons Among Biologic Therapies for Urticaria

Variable	Omalizumab[45]	Ligelizumab[46]	Dupilumab[47]	Lirentelimab[48,49]
FDA approval status	Approved	No	No (case series, current phase 2a clinical trials)	No (phase 2 clinical trials)
Age approved	≥12 y	N/A (studies ≥12 y)	N/A (youngest in case series was 18 y)	N/A (youngest in case series was 18 y)
Mechanism of action	Anti-IgE - Cannot recognize CD23-bound IgE	Anti-IgE - Higher affinity than omalizumab (~40 fold) - Can recognize CD23-bound IgE - More potently inhibits mast cell and basophil activation - Mice models: more effectively inhibits anaphylaxis	Anti–IL-4/13Ra - Case series evaluated 6 patients who failed omalizumab - All 5 out of 6 (1 did not report urticaria status) responded with dupilumab	Siglec-8 Inhibitor
Route	SC	SC	SC	SC
Frequency	Every 2-4 wk	Every 4 wk	Every 2 wk	Every 4 wk
Dose	150-300 mg	240 mg	600 mg loading dose, 300 mg thereafter	mg/kg (weight-based) dosing
Biomarkers	None	None	None	None
Symptom Score and quality of life improvements vs placebo (statistically significant)	Yes	Yes (and more than Omalizumab)	Yes	Yes (in both omalizumab-naive and omalizumab nonresponsive patients)

Abbreviations: FDA, Food and Drug Authority; IgE, immunoglobulin E; IL, interleukin; N/A, not applicable; SC, subcutaneous.

associated with an overall annual rate reduction of asthma exacerbations by 55.7% and by 39% in patients with eosinophil count at baseline of less than 150 cells/μL.[43]

IL-33 is another interleukin of interest. IL-33 is an epithelial-derived alarmin that is released in response to inhaled allergens and tissue injury. IL-33 can activate both T2-low and T2-high pathways and lead to an up-regulation of tumor necrosis alpha, interferon gamma, IL-5, IL-6, IL-9, and IL-13. Astegolimab is an IL-33 receptor inhibitor that targets soluble interleukin 1 receptor-like 1 receptors on parenchymal and inflammatory cells such as innate lymphoid immune cells, T cells, eosinophils, mast cells, dendritic cells, macrophages, and endothelial cells. In the phase 2b ZENYATTA study, astegolimab was evaluated in patients with severe asthma. Compared with placebo, astegolimab 490 mg subcutaneous every 4 weeks led to a 43% relative reduction in asthma exacerbation rate with a number needed to treat of 8.77. In a subgroup analysis of patients with eosinophil count less than 300 cells/μL, astegolimab 490 mg had a 53.6% relative reduction in asthma exacerbation rate compared with placebo with a number needed to treat of 2.63.[44] Astegolimab, like tezepelumab, may become an option in the future for patients with T2-low or T2-high asthma.

Because of the success of these biologics, blockers of other alarmins, new anti-IgE molecules, and longer lasting IL-5 blockers are in clinical development.[45] It is hoped that these advances will lead to better and more cost-effective therapies for patients with moderate-to-severe asthma of both T2-high and T2-low patients. In addition, future therapeutics should target and reverse airway remodeling with immunomodulation leading to asthma remission, which, at present, none of the current biologics have achieved.

Urticaria

Chronic idiopathic/spontaneous urticaria (CIU) is defined as recurrent episodes of hives and/ or angioedema for longer than 6 weeks. These symptoms can considerably affect a patient's quality of life. First-line therapy for CIU consists of high-dose second-generation antihistamines; however, more than 50% of patients do not respond or do not achieve an acceptable level of control of their symptoms. Other adjunct therapies, such as dapsone, tacrolimus, and cyclosporin can have severe adverse effects, such as bone marrow suppression or kidney injury; thus, their use should be avoided. Biologic therapies provide an ideal treatment option with minimal adverse effects and excellent response rates.[1] Anti-IgE, anti–IL-4/13, and anti–IL-1 therapies are currently the most promising biologics for CIU.

Omalizumab and Ligelizumab

Anti-IgE therapy has been the most thoroughly studied for use in CIU. One possible mechanism involved in CIU is the development of autoantibodies that target IgE or the α-chain of FcεR1. Omalizumab and Ligelizumab can simultaneously inhibit both processes by triggering a reduction in serum IgE, leading to the subsequent induction of internalization of FcεR1 on mast cells and basophils.[1]

Omalizumab's use in urticaria was thoroughly discussed in our previous review article[1]; thus we will mainly focus on new insights. Omalizumab is currently FDA-approved for patients 12 years and older. More than 50% of patients experienced complete resolution of their hives with the 300-mg dose subcutaneously every 4 weeks, and phase 3 trials found improvement in quality-of-life scores. It has also been found to help with coexisting angioedema. In patients with autoantibodies, the clinical effects can be delayed. Omalizumab has also been found in smaller studies to be beneficial for patients with urticarial vasculitis and inducible urticarias.[1]

Ligelizumab has an almost 40-fold higher affinity for IgE given its slower off-loading time. It more potently inhibits IgE binding to FcεR1, and unlike omalizumab, it can recognize CD23-bound IgE. It also more potently inhibits mast cell and basophil activation, which would likely explain its higher effectiveness at inhibiting anaphylaxis in mice models. The implications of this for idiopathic anaphylaxis and other mast cell disorders are exciting. Ligelizumab outperformed omalizumab in quality of life and urticaria activity scores at all doses studied (24 mg, 72 mg, and 240 mg, with the most benefit seen at 240 mg) with monthly dosing. It is not yet FDA-approved, but phase 3 trials will soon be completed.[46]

Dupilumab

Dupilumab indirectly lowers IgE levels, and thus, triggers internalization of FcεR1 by blocking the IL-4α receptor and subsequent IL-4/13 signaling.[47] This inhibits class switching of immunoglobulin M to IgE. High serum levels of IL-4 and IL-13 have been reported in some patients with CIU, whereas others have a higher level of cells expressing IL-4 at the mRNA level on skin biopsy. Thus, decreasing IL-4/13 signaling may be beneficial in these patients, but the point-of-care biomarkers to predict responsiveness is lacking. In a 6-patient case study with CIU unresponsive to omalizumab, patients were started on dupilumab (600 mg loading dose, subsequent 300 mg dosing every 2 weeks) with 5 of 6 responding (1 did not report their urticaria status at the end of the study). Clinical trials exploring the use of dupilumab for both CIU and chronic inducible urticaria are ongoing.[47] A recent press release indicated that a phase 3 trial met its primary end points and all key secondary end points at 24 weeks, illustrating a nearly doubled reduction in itch and urticaria activity scores in patients treated with dupilumab (https://www.sanofi.com/en/media-room/press-releases/2021/2021-07-29-07-00-00-2270858).

Lirentelimab

Lirentelimab is a Siglec-8 inhibitor that simultaneously inhibits mast cell activation and triggers apoptosis of eosinophils. In phase II trials, lirentelimab improved response in both omalizumab-naive patients and omalizumab-resistant patients. It has also exhibited efficacy in inducible urticarias as well.[48,49]

Anakinra, Canakinumab, Rilonacept

Currently, anti-IL1 therapy is only indicated for patients with urticaria in the setting of autoinflammatory syndromes in the cryopyrin-associated periodic syndromes spectrum. The current FDA-approved options are anakinra (recombinant human IL-1Ra antagonist), canakinumab (humanized anti–IL-1β monoclonal antibody), and rilonacept (a soluble-decoy receptor that blocks IL-1β signaling). Trials have also revealed favorable data for the use of anakinra and canakinumab in Schnitzler syndrome.[1]

Other Agents Currently in Development

Other monoclonal antibodies on the horizon for CIU include anti–IL-5 and anti–IL-5R agents like mepolizumab and benralizumab respectively, tezepelumab, and the CD117 inhibitor Celldex. All are in various stages of development, ranging from phase I to phase II trials.[48]

Which to Choose?

There are currently no commercially available biomarkers to accurately predict the responsiveness to biologics for CIU, but low IgE levels have been correlated with favorable responses to omalizumab. Because omalizumab is the only FDA-approved option, it is currently the preferred choice. Patients who fail omalizumab may benefit from dupilumab. Those patients who also have coexisting idiopathic anaphylaxis or a possible mast cell disorder may benefit from omalizumab. Ligelizumab could be a good alternative agent for both

Table 2
Comparisons Among Biologic Therapies for Nasal Polyps

Variable	Dupilumab[50]	Omalizumab[51]	Mepolizumab[18]	Benralizumab[52]
FDA approval status	Approved	Approved	Approved	No (Phase III)
Age approved	≥18 y	≥18 y	N/A (studies ≥18 y)	N/A
Mechanism of Action	Anti–IL-4/13Ra	Anti-IgE	Anti–IL-5	Anti–IL-5Ra
Route	SC	SC	IV or SC	SC
Frequency	Every 2 wk	Every 2-4 wk	Every 4 wk	Every 4 wk for the first 3 doses, every 8 wk after that
Dose	600 mg loading dose, subsequent 300 mg	Weight-based (mg/kg)	750 mg (IV), 100 mg (SC)	30 mg
Biomarkers	None	IgE 30-1500 IU/mL	Eos ≥150	N/A (no eosinophil cutoff was used for enrollment in one, ≥300 in another)
Reduction in Polyp Size	Yes	Yes	Yes (irrespective of comorbid asthma or N-ERD)	Yes - Note: studies were done in the context of coexisting severe eosinophilic asthma
Reduction in Need for Surgery	Yes	No statistically significant decrease	Yes	Yes
Steroid sparing effect	Yes	No statistically significant decrease	Yes	Yes
Symptom Score and quality of life improvements vs placebo (statistically significant)	Yes (SNOT-22, UPSIT) Dupilumab had consistently greater improvement in key CRSwNP outcomes vs omalizumab at wk 24[a]	Yes (SNOT-22, UPSIT, and TNSS)	Yes (SNOT-22, VAS)	Yes (SNOT-22, NRS, endoscopic nasal polyp score, Lund-Mackay CT score)

Abbreviations: CRSwNP, chronic rhinosinusitis with nasal polyposis; CT, computed tomography; FDA, Food and Drug Authority; IgE, immunoglobulin E; IL, interleukin; IV, intravenous; N-ERD, non-steroidal anti-inflammatory drug-exacerbated respiratory disease; N/A, not applicable; SC, subcutaneous; SNOT-22, sino-nasal outcome test; TNSS, total nasal symptom score; UPSIT, University of Pennsylvania Smell Identification Test; VAS, visual analog scale.
[a]References [50,51].

disorders should phase 3 studies confirm phase 2 data. For suspected autoinflammatory syndrome–related urticaria, anti–IL1 therapy is the ideal choice (Table 2).

Nasal Polyps

In patients with nasal polyps and associated tissue eosinophilia, intranasal glucocorticoid therapy is an effective option. However, in patients in whom intranasal glucocorticoid therapy is insufficient, recurrent oral glucocorticoid therapy, although effective, is not ideal given the plethora of potential adverse effects and long-term health complications. Elevated tissue eosinophilia in patients with nasal polyp is also associated with a higher chance of recurrence after surgical removal. These patients have also been found to have elevated IL-4, IL-5, and IL-13 levels, and elevated mucosal IgE.[1]

Dupilumab

Dupilumab is currently FDA-approved for patients with nasal polyp aged 18 years or older either as a pre- or postsurgical option. It requires a one-time 600-mg loading dose with subsequent 300 mg 2-weekly dosing. No biomarkers are required for its use. In multiple studies, it was found to reduce polyp size, prevent the need for surgery, and had a corticosteroid-sparing effect. In addition, it led to an improvement in symptom and quality-of-life scores. It is also effective in patients with coexisting T_H2 asthma.[1,50]

Omalizumab

Omalizumab is also FDA-approved for patients with nasal polyp aged 18 years or older. The biomarker used to guide therapy is an IgE level between 30 and 1500 IU/mL. Unlike dupilumab, the dosing is weight-based (mg/kg) and it is administered every 2 to 4 weeks. Like dupilumab, it can be used as a pre- or postsurgical option. Omalizumab also exhibited a significant reduction in the need for surgery (P = .02) and had a non-statistically significant corticosteroid-sparing effect. Omalizumab did lead to improvement in symptom and quality-of-life scores. Omalizumab could be used in patients with coexisting T_H2 asthma, particularly with an elevated IgE level.[51]

Mepolizumab and Benralizumab

Mepolizumab is now FDA-approved and benralizumab is currently in phase 3 clinical trials for nasal polyposis. The study SYNAPSE[18] was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial of 100 mg mepolizumab (given subcutaneously) or placebo once every 4 weeks, in addition to standard of care. Total endoscopic nasal polyp score significantly ($P < 0.001$) improved at week 52 from baseline with mepolizumab vs placebo and nasal obstruction during weeks 49 to 52 also significantly ($P < 0.001$) improved. Mepolizumab reduced the need for nasal surgery and systemic corticosteroid use and improved sinonasal symptoms and health-related quality of life with an acceptable safety profile. Improvements were greater in patients with higher blood eosinophil levels.[18]

In preliminary studies, benralizumab exhibited a reduction in polyp size and need for surgery and a corticosteroid-sparing effect. However, it is important to note that mepolizumab exhibited a benefit irrespective of comorbid asthma or NSAID-exacerbated respiratory disease, whereas benralizumab has only been evaluated in the setting of severe eosinophilic asthma, but phase 3 data are pending.[52]

Which to Choose?

No specific biomarkers have enabled a better selection of a particular agent for the treatment of chronic rhinosinusitis with nasal polyps (Table 3). However, only mepolizumab exhibited improvements in patients related to blood eosinophil levels. Omalizumab has been suggested to work better in patients with IgE secondary to Staphylococcus enterotoxin.[53] In a recently done indirect meta-analysis, the authors concluded that the effects of dupilumab were greater than those seen for omalizumab.[54] However, direct comparative studies between the biologics in the same patients are lacking, but are planned. The choice of a specific biologic might also be influenced by comorbid conditions treated by the biologic.[55]

Atopic Dermatitis

Atopic dermatitis is one of the more life-impairing and potentially disfiguring diseases allergists treat. Key cytokines involved in the

Table 3
Comparisons Among Biologic Therapies for Atopic Dermatitis

Variable	Dupilumab[1]	Tezepelumab[58]	Fezakinumab[59]	Nemolizumab[60,61]	Tralokinumab[56]	Lebrikizumab[57]
FDA approval status	Yes	No (phase III Trials)	No (phase 2a trial complete)	No	No (phase 3 clinical trials)	No (phase 2b clinical trial)
Age approved	≥6 y	N/A	N/A (≥18 y studies)	N/A	N/A	N/A
Mechanism of action	Anti–IL-4/13Ra	Anti-TSLP	Anti–IL-22	Anti–IL-31Ra	Anti–IL-13	Anti–IL-13
Route	SC	SC	IV	SC	SC	SC
Frequency	Every 2 wk	Every 2 wk	Every 2 wk	Every 4 wk	Every 2 wk	Every 2-4 wk
Dose	600 mg loading dose, 300 mg thereafter	280 mg	600 mg loading dose, 300 mg thereafter	60 mg	300 mg	125 mg every 4 weeks (250-mg LD), 250 mg every 4 wk (500-mg LD), or 250 mg every 2 wk (500-mg LD at baseline and wk 2)
Biomarkers	None	N/A	N/A	N/A	N/A	N/A
Steroid sparing effect	N/A (but the addition of TCS lead to even more improvement)	N/A (but the addition of TCS lead to even more improvement)	N/A (It was not mentioned in the study if topical steroids were allowed to be continued)	N/A (but the addition of TCS lead to even more improvement)	Yes (most did not need rescue medication, including topical steroids, by wk 16)	Yes (3 times less use than placebo group)
Symptom Score and quality of life improvements vs placebo (statistically significant)	Yes (EASI and extent of BSA involvement)	Yes (EASI-50 especially) but was in addition to topical steroids	Yes (SCORAD)	Yes (VAS for pruritis)	Yes (pruritus, sleep interference, Dermatology Life Quality Index, EASI, SCORAD, and patient-oriented eczema measure)	Yes but with the 250 mg Q2 weeks only (EASI, IGA, and puritus)

Abbreviations: BSA, body surface area; EASI, eczema area and severity index; FDA, Food and Drug Authority; IGA, investigator global assessment; IL, interleukin; IV, intravenous; LD, loading dose; N/A, not applicable; SC, subcutaneous; SCORAD, SCORing Atopic Dermatitis; TCS, topical corticosteroids; TSLP, thymic stromal lymphopoietin; VAS, visual analog scale.

pathogenic process include IL-4, IL-5, and IL-13. Other potential cytokine targets currently being studied are TSLP, IL-12, IL-17, IL-22, and IL-31.[1]

Dupilumab

Dupilumab is currently the only FDA-approved biologic for patients with atopic dermatitis aged 6 years and older. Studies are currently ongoing for children between 2 and 5 years of age. It requires a one-time loading dose of 600 mg subcutaneous then 300 mg every 2 weeks thereafter. It does not require any biomarkers for approval. Its concomitant use with topical corticosteroids leads to even greater improvement in symptoms. It resulted in substantial improvements in quality of life and symptom scores.[1]

Interleukin-13 blockers

Many studies are evaluating the therapeutic potential of monoclonal antibodies against IL-13 for atopic dermatitis. Tralokinumab exhibited statistically significant ($P = 0.002$) improvements over placebo in 2 phase 3 clinical trials recently completed.[56] The efficacy and safety of lebrikizumab in adults with moderate-to-severe atopic dermatitis was reported in a phase 2b randomized clinical trial.[57]

Tezepelumab

A phase 2a trial of tezepelumab, an anti-TSLP monoclonal antibody, in adults with moderate-to-severe atopic dermatitis found some promising results. However, a second phase 2 trial for atopic dermatitis was discontinued owing to a lack of efficacy.[58]

Fezakinumab

Fezakinumab, an anti–IL-22 agent, has been evaluated in phase 2a clinical trials for atopic dermatitis. One drawback of this therapy is that it is only currently available as an intravenous formulation. Like dupilumab, it requires a 600 mg loading dose and 300 mg every 2 weeks thereafter. It was not mentioned in the study whether concomitant treatments were allowed to be continued, but it did lead to improvement in symptom and quality-of-life scores.[59]

Nemolizumab

Nemolizumab blocks anti–IL-31Rα and is currently being evaluated as a possible atopic dermatitis therapy. Its dosing is 60 mg subcutaneously every 4 weeks. It led to improvement in pruritus (primary end point) and quality-of-life scores.[60,61]

Which to Choose?

Currently, dupilumab is the only FDA-approved biologic for atopic dermatitis, but fezakinumab and nemolizumab are promising options (Table 4). However, given the efficacy and safety profile of dupilumab, this is currently the best and only option.

Food Allergy

The newest and potentially most exciting application for biologics is the realm of food allergy. Multiple studies are currently underway evaluating the ability of biologics to help increase the amount patients with food allergy can consume before eliciting a reaction. Other studies are evaluating biologic therapy in conjunction with oral immunotherapy (OIT). The results seem to be very promising so far.

Omalizumab and Ligelizumab

There have been at least 3 peanut studies and 1 multifood non-OIT study evaluating omalizumab's ability to allow patients to have a higher threshold for reactivity to the offending food.[62-68] The peanut studies found an increase in the tolerated peanut dose, but 1 was terminated early because of 2 severe reactions during the entry food challenges. However, the increases in doses tolerated were substantial, with 1 study reporting an increase from 80 mg to 10,000 mg (approximately 35 peanut kernels) at week 24. The multifood data reported similar results, with 1 study[62] reporting a greater than eight-fold increase in tolerated milk, egg, wheat, and hazelnut in the omalizumab vs the placebo group. A total of 70% of patients were

Table 4
Comparisons Among Biologic Therapies for Food Allergy

Variable	Omalizumab[62-68]	Dupilumab (no published data, clinical trial IDs are indicated in the text)	Etokimab[69]
FDA approval status	No	No	No
Age approved	N/A (8-44 y)	N/A	N/A
Mechanism of action	Anti-IgE	Anti–IL-4/13Ra	Anti–IL-33
Route	SC	SC	N/A
Frequency	Every 2-4 wk	N/A	N/A (after 1 injection)
Dose	N/A	N/A	N/A
Biomarkers	N/A (Fiocchi et al[62]: total IgE, 208-1491)	N/A	N/A
Amount of target food able to ingest	Various studies: - Sampson et al[56] (peanut): Increase threshold dose vs baseline, but the study was terminated owing to 2 severe reactions during entry DBPCFC - Savage[57] (peanut): Increased median tolerated dose from 80 mg to 6500 mg at wk 5, 4 tolerated full 10,000 mg at wk 24 - Brandström et al[65] (peanut): 65% able to tolerate full dose (2800 mg), all ingested at least 840 mg - Fiocchi[62] (multifood allergic/single if failed OIT): the mean increase in threshold from 1013 mg to 8728 mg (milk, egg, wheat, hazelnut), 70% tolerated complete OFC dose and able to reintroduce into the diet without OIT OUtMATCH study pending[a]	Studies in the works: - Dupilumab monotherapy in patients with peanut allergy: recruiting, goal = pass a low dose DBPCFC - Dupilumab patients with multifood allergy (vs omalizumab): recruiting; goal = passing 1043 mg DBPCFC at the end of wk 44 - Dupilumab + multifood allergic atopic dermatitis patients: recruiting, goal = change in eliciting dose after 28 wk	Results after a single dose (peanut): - 73% passed CTD 275 mg on day 15 vs 0% at baseline (P = .008), 57% on day 45 vs 0% at baseline (placebo stayed at 0% for both) - 47% passed CTD 375 mg on day 15 vs 0% at baseline, 29% on day 45 vs 0% at baseline (placebo stayed at 0% for both) - One patient was able to tolerate ~ 500 mg on day 15
Outcomes in conjunction with OIT	Various studies: - Wood[59] (milk): 88.9% vs 71.4% (placebo) passed 10g desensitization OFC at month 28 (P = .18); at month 32 (16 wk off OMA and 8 wk of OIT), 48.1% vs 35.7% (placebo) had SU (P = 0.42); 2.1% vs 16.1% (placebo) had symptoms during escalation (P < .001); dose reactions needing treatment 0.0% vs 3.8% (placebo, P < .001) - MacGinnitie[60] (peanut): 79.3% vs 12.5% (placebo) tolerated 2000 mg 6 wk off omalizumab (P < .001); 75.9% vs 1.5% (placebo) tolerated 4000 mg off omalizumab (P < .001); reaction rates not significantly different, but omalizumab patients were exposed to higher peanut doses - Andorf[68] (multifood): 83% vs 33% (placebo) tolerated 2 g of ≥2 foods at 36 wk (P = –.004); 27% vs 68% (placebo) median per-subject percentage of OIT doses associated with adverse events (P = .008) OUtMATCH study pending[a]	Studies in the works: - Dupilumab in conjunction with peanut OIT: active but not recruiting, goal = pass 2044 mg DBPCFC at wk 28 - Dupilumab in conjunction with milk OIT: not yet recruiting, goal = pass 2040 mg DBPCFC at wk 18	N/A

Abbreviations: CTD, cumulative tolerated dose; DBPCFC, double-blind placebo-controlled food challenge; FDA, Food and Drug Authority; ID, identification; IgE, immunoglobulin E; IL, interleukin; N/A, not applicable; OFC, oral food challenge; OIT, oral immunotherapy; OMA, omalizumab; OUtMATCH, omalizumab as monotherapy and as adjunct therapy to multi-allergen OIT in food allergic children and adults; SC, subcutaneous; SU, spontaneous urticaria.
[a]References [50,51].

able to complete an oral food challenge dose of greater than 7000 mg and able to reintroduce the food into their diet without OIT. The omalizumab as monotherapy and as adjunct therapy to multi-allergen OIT in food allergic participants (OUtMATCH) study funded by the National Institutes of Health is currently enrolling. This study is evaluating whether omalizumab as monotherapy is as good or better than omalizumab plus OIT. Because the previous studies with omalizumab were not often designed as double-blind, randomized controlled studies in large cohorts, the OUtMATCH trial will be important in determining the use of omalizumab as monotherapy or in conjunction with OIT.[62-68]

As described above, ligelizumab seems to have a better ability to block mast cell and basophil-mediated events than omalizumab. Phase 3 studies will begin shortly exploring the use of this agent as monotherapy for food allergy.

Dupilumab

There are no published data available for dupilumab and food allergy, but there are currently several studies underway evaluating its effectiveness (clinical trial identification numbers (IDs), NCT03682770, NCT03793608, NCT04148352, NCT04462055, NCT03679676). Most are to evaluate if the dose threshold eliciting symptoms is increased, but 1 exciting study is looking at whether dupilumab in patients with multifood allergies and atopic dermatitis have an increase in eliciting dose after 28 weeks (clinical trial ID, NCT04462055). There are currently 2 multifood studies underway (clinical trial IDs, NCT04462055, NCT03679676) and 1 peanut study (clinical trial ID, NCT03682770). As for food OIT-dupilumab studies, there are currently 2 studies underway, 1 with peanut OIT (clinical trial ID, NCT03682770) and another with milk OIT (clinical trial ID, NCT04148352). Finally, another study is exploring omalizumab pretreatment followed by OIT plus dupilumab (clinical trial ID, NCT03679676).

Etokimab

Etokimab is an anti–IL-33 monoclonal that was evaluated in 20 patients with peanut allergy (5 placebo and 15 verum). After a single dose, an impressive 73% passed a 275-mg challenge on day 15 vs 0%

Table 5
Comparisons Among Biologic Therapies for Eosinophilic Esophagitis

Variable	Omalizumab[70]	Dupilumab[71]	Lirentelimab[72]	Mepolizumab[73,74]	Reslizumab[76]	Benralizumab[73]	Dectrekumab (QAX576)[77]	RPC4046[78]
FDA approval status	No	No (phase 2)	No	No	No	No (phase 2, but not EoE specifically, HES with 7 patients having GI involvement)	No	No
Age approved	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Mechanism of action	Anti-IgE	Anti–IL-4/13Ra	Anti–Siglec-8	Anti–IL-5	Anti–IL-5	Anti–IL-5Ra	Anti–IL-13	Anti–IL-13
Route	SC	SC	N/A	IV	IV	SC	IV	N/A
Frequency	Every 4 wk	wk	N/A	N/A	N/A	Every 4 wk	N/A	N/A
Dose	N/A	300 mg	N/A	750 mg × 2 doses >1500 mg × 2 doses 0.55, 2.5, 10 mg/kg	1, 2, or 3 mg/kg	30 mg	N/A	N/A
Biomarkers	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15
Reduction in eosinophils	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Symptom score and quality of life improvements vs placebo (statistically significant)	Mild improvement	Yes	No (high dose, $P = .001$)	N/A	Yes	N/A	N/A	No (high dose, $P = .001$)

Abbreviations: EoE, eosinophilic esophagitis; FDA, Food, and Drug Authority; GI, gastrointestinal; HES, hypereosinophilic syndrome; IgE, immunoglobulin E; IL, interleukin; N/A, not applicable.

on day 1. A total of 47% passed a 375-mg challenge on day 15 vs 0% at baseline, and 29% on day 45 vs 0% at baseline. One patient was able to tolerate 500 mg on day 15.[69]

Which to Choose?

Currently, it is too early to make recommendations as to which agent to choose when it comes to food allergy (Table 5). Omalizumab is indeed promising, but depending on the outcome of studies evaluating omalizumab and other agents including dupilumab, ligelizumab, and anti-alarmins, it is difficult to predict the role of biologics either as monotherapy or in conjunction with immunotherapy. Given the current estimate of up to 32 million Americans having food allergy, the health care system would not support the use of biologics for every patient. Identifying appropriate candidates will be key.

Eosinophilic Esophagitis

Eosinophilic esophagitis (EoE), in theory, seems to be the perfect target for biologic therapies, especially anti–IL-5 and anti–IL-5Rα. However, data from previous trials have not been very promising. Nevertheless, several agents are being evaluated for EoE at this time.

Omalizumab

Omalizumab's foray into EoE was, unfortunately, not very impressive. It did not exhibit any reduction in eosinophil counts on repeat biopsy and only lead to mild improvement in symptom and quality-of-life scores.[70]

Dupilumab

Dupilumab was evaluated in a phase 2 study in patients with EoE. Unlike its usual dosing schedule, it was given 300 mg weekly. It did lead to a reduction in eosinophil levels and improvement in symptom and quality-of-life scores.[71] Unpublished phase 3 data look promising as well.

Lirentelimab

Lirentelimab, a siglec-8 inhibitor, is currently being evaluated for use in EoE and eosinophilic gastroenteritis in general. Siglec-8 is expressed on mast cells, eosinophils, and basophils, and when targeted, leads to apoptosis of eosinophils and prevents the release of stored and newly formed mediators from mast cells. The inhibition of these mediators, in turn, decreases the recruitment of local eosinophils. In clinical trials, it led to a reduction in tissue eosinophils and a modest improvement in symptom and quality-of-life scores.[72]

Mepolizumab, Reslizumab, and Benralizumab

All 3 IL-5 blockers are currently being studied as potential EoE therapies except for benralizumab, which was studied in patients with hypereosinophilic syndrome, 7 of whom had gastrointestinal involvement.[73] However, 2 of the agents, mepolizumab, and reslizumab, were studied as intravenous options. All 3 lead to an expected reduction in tissue eosinophil levels and reslizumab lead to improvement in symptom and quality-of-life scores (this was not evaluated in the mepolizumab and benralizumab studies).[73-76]

Dectrekumab and RPC4046

Dectrekumab (intravenous agent) and RPC4046 are 2 new anti–IL-13 agents currently being studied for use in EoE. Both lead to a reduction in tissue eosinophil counts. Symptom and quality-of-life

Table 6
Comparison of Biologic Therapies for Asthma[1]

Variable	Omalizumab	Mepolizumab	Reslizumab	Dupilumab	Benralizumab
FDA approval status	Yes	Yes	Yes	Yes	Yes
Age approved	≥6 y	≥6 y	≥18 y	≥12 y	≥12 y
Mechanism of action	Anti-IgE	Anti–IL-5	Anti–IL-5	Anti–IL-4/13Ra	Anti–IL-5Ra
Route	SC	SC	IV	SC	SC
Frequency	Every 2-4 wk (weight-based and pretreatment IgE)	Every 4 wk	Every 4 wk	Every 2 wk	Every 4 wk for 3 doses and then every 8 wk
Dose	150-375 mg	40-100 mg (on the basis of age)	3 mg/kg infusion	400-600 mg initial dose followed by 200-300 mg	30 mg
High level of evidence for measured outcomes[36]	Reduced exacerbations, daily OCS dose	Reduced exacerbations, daily OCS dose, and rescue medication use	Reduced exacerbations, controller, and rescue medication use, improved QOL	Reduced exacerbations, daily OCS dose, and improved FEV1	Reduced exacerbations, daily OCS dose, and controller medications, and improved QOL

Abbreviations: FDA, Food and Drug Authority; FEV1, forced expiratory volume in 1 second; IgE, immunoglobulin E; IL, interleukin; IV, intravenous; OCS, oral corticosteroid; QOL, quality of life; SC, subcutaneous.

scores were not evaluated for Dectrekumab, but they were for RPC4046, which exhibited improvement in these scores.[77,78]

Other Agents

Anti–IL-15 and anti–tumor necrosis factor alpha are 2 other classes of agents being explored for the treatment of EoE, but there are currently no published data.

Which to Choose?

It is too early to recommend a biologic agent for EoE, but dupilumab and reslizumab seem to have the most promising data in terms of improving both tissue eosinophil numbers and symptom and quality-of-life scores (Table 6). However, reslizumab and many of the other agents being evaluated for EoE are intravenous preparations, which may limit their use. Benralizumab and liretelimab directly lead to eosinophil apoptosis, which is appealing and limits the chance for the rebound in eosinophils that can occur with agents mainly targeting eosinophil recruitment.

Conclusion

The landscape for biologic therapy in allergic diseases is vast and rapidly expanding. Although the number of choices can be daunting, the fact that the options can provide tailored therapy for so many patients is a life changing benefit. However, there need to be more studies evaluating the cost effectiveness of these therapies, appropriate candidates for these therapies, and selective biomarkers to better predict therapeutic responsiveness. Having so many agents available provide valuable tools for better understanding the biology of these disorders. However, given the wide prevalence of allergic diseases and the cost of these biologics, they must only be used for appropriately selected patients. Furthermore, because none of these agents have exhibited the ability to cure these diseases, we need to understand how best to determine the course of therapy regarding dosing, corticosteroid-sparing effects, duration of therapy, and when and how to restart or switch biologics.

References

1. Saco TV, Pepper A, Casale TB. Uses of biologics in allergic diseases: what to choose and when. *Ann Allergy Asthma Immunol*. 2018;120(4):357–366.
2. Holguin F, Cardet JC, Chung KF, et al. Management of severe asthma: a European Respiratory Society/American Thoracic Society guideline. *Eur Respir J*. 2020;55:(1) 1900588.
3. Woodruff PG, Bhakta NR, Fahy JV. Asthma. In: Broaddus VC, Mason RJ, Ernst JD, eds. *Murray and Nadel's Textbook of Respiratory Medicine*. Philadelphia, PA: Elsevier; 2016:713–730.e717.
4. Muraro A, Lemanske RF, Hellings PW, et al. Precision medicine in patients with allergic diseases: airway diseases and atopic dermatitis—PRACTALL document of the European Academy of Allergy and Clinical Immunology and the American Academy of Allergy. Asthma & Immunology *J Allergy Clin Immunol*. 2016;137(5):1347–1358.
5. Gill MA, Liu AH, Calatroni A, et al. Enhanced plasmacytoid dendritic cell antiviral responses after omalizumab. *J Allergy Clin Immunol*. 2018;141(5):1735–1743.e9.
6. Busse W, Corren J, Lanier BQ, et al. Omalizumab, anti-IgE recombinant humanized monoclonal antibody, for the treatment of severe allergic asthma. *J Allergy Clin Immunol*. 2001;108(2):184–190.
7. Casale TB, Win PH, Bernstein JA, et al. Omalizumab response in patients with chronic idiopathic urticaria: insights from the XTEND-CIU study. *J Am Acad Dermatol*. 2018;78(4):793–795.
8. Brusselle G, Michils A, Louis R, et al. "Real-life" effectiveness of omalizumab in patients with severe persistent allergic asthma: the PERSIST study. *Respir Med*. 2009;103(11):1633–1642.
9. Casale TB, Luskin AT, Busse W, et al. Omalizumab effectiveness by biomarker status in patients with asthma: evidence from PROSPERO, a prospective real-world study. *J Allergy Clin Immunol Pract*. 2019;7(1):156–164.e1.
10. Yu C, Wang K, Cui X, et al. Clinical efficacy and safety of omalizumab in the treatment of allergic rhinitis: a systematic review and meta-analysis of randomized clinical trials. *Am J Rhinol Allergy*. 2020;34(2):196–208.
11. Long A, Borro M, Sampath V, Chinthrajah RS. New developments in non-allergen-specific therapy for the treatment of food allergy. *Curr Allergy Asthma Rep*. 2020;20(1):3.
12. Celebi Sozener Z, Gorgulu B, Mungan D, et al. Omalizumab in the treatment of eosinophilic granulomatosis with polyangiitis (EGPA): single-center experience in 18 cases. *World Allergy Organ J*. 2018;11(1):39.
13. Hanania NA, Chipps BE, Griffin NM, Yoo B, Iqbal A, Casale TB. Omalizumab effectiveness in asthma-COPD overlap: post hoc analysis of Prospero. *J Allergy Clin Immunol*. 2019;143(4):1629–1633.e2.
14. Genentech, Inc. US Food and Drug Administration. Xolair (omalizumab). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/103976s5225lbl.pdf. Accessed May 29, 2021.
15. GlaxoSmithKline, LLC. U.S. Food and Drug Administration. Nucala (mepolizumab). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/nda/2019/761122Orig1s000Lbl.pdf. Accessed May 29, 2021.
16. Ortega HG, Liu MC, Pavord ID, et al. Mepolizumab treatment in patients with severe eosinophilic asthma. *N Engl J Med*. 2014;371(13):1198–1207.
17. Bel EH, Wenzel SE, Thompson PJ, et al. Oral glucocorticoid-sparing effect of mepolizumab in eosinophilic asthma. *N Engl J Med*. 2014;371(13):1189–1197.
18. Han JK, Bachert C, Fokkens W, et al. Mepolizumab for chronic rhinosinusitis with nasal polyps (SYNAPSE): a randomised, double-blind, placebo-controlled phase 3 trial. *Lancet Respir Med*. 2021;2600(21):1–13.
19. Tolebeyan A, Mohammadi O, Vaezi Z, Amini A. Mepolizumab as possible treatment for allergic bronchopulmonary aspergillosis: a review of eight cases. *Cureus*. 2020;12(8):e9684.
20. Pavord ID, Chanez P, Criner GJ, et al. Mepolizumab for eosinophilic chronic obstructive pulmonary disease. *N Engl J Med*. 2017;377(17):1613–1629.
21. Castro M, Mathur S, Hargreave F, et al. Reslizumab for poorly controlled, eosinophilic asthma: a randomized, placebo-controlled study. *Am J Respir Crit Care Med*. 2011;184(10):1125–1132.
22. 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(4):799–810.
23. Mukherjee M, Aleman Paramo F, Kjarsgaard M, et al. Weight-adjusted intravenous reslizumab in severe asthma with inadequate response to fixed-dose subcutaneous mepolizumab. *Am J Respir Crit Care Med*. 2018;197(1):38–46.
24. Nsouli S. P509 reslizumab an interleukin-5 antagonist monoclonal antibody for uncontrolled chronic rhinosinusitis with nasal polyps. *Ann Allergy Asthma Immunol*. 2020;125(5):S49–S50.
25. Teva Pharmaceutical Industries, Ltd, US Food and Drug Administration. Cinqair. (reslizumab). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2016/761033lbl.pdf. Accessed June 3, 2021.

26. Sanofi Biotechnology and Regeneron Pharmaceuticals, Inc, US Food and Drug Administration. Dupixent (dupilumab). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/761055s007lbl.pdf. Accessed June 13, 2021.
27. Castro M, Corren J, Pavord ID, et al. Dupilumab efficacy and safety in moderate-to-severe uncontrolled asthma. *N Engl J Med*. 2018;378(26):2486–2496.
28. Rabe KF, Nair P, Brusselle G, et al. Efficacy and safety of dupilumab in glucocorticoid-dependent severe asthma. *N Engl J Med*. 2018;378(26):2475–2485.
29. Mustafa SS, Vadamalai K. Dupilumab increases aspirin tolerance in aspirin-exacerbated respiratory disease. *Ann Allergy Asthma Immunol*. 2021;126(6):738–739.
30. AstraZeneca Pharmaceuticals LP, US Food and Drug Administration. Fasenra (benralizumab). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/761070s000lbl.pdf. Accessed June 13, 2021.
31. FitzGerald JM, Bleecker ER, Nair P, et al. Benralizumab, an anti-interleukin-5 receptor α 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(10056):2128–2141.
32. Bleecker ER, FitzGerald JM, Chanez P, et al. Efficacy and safety of Benralizumab for patients with severe asthma uncontrolled with high-dosage inhaled corticosteroids and long-acting β2-agonists (Sirocco): a randomised, multicentre, placebo-controlled phase 3 trial. *Lancet*. 2016;388(10056):2115–2127.
33. Nair P, Wenzel S, Rabe KF, et al. Oral glucocorticoid-sparing effect of benralizumab in severe asthma. *N Engl J Med*. 2017;376(25):2448–2458.
34. Tat TS, Cilli A. Omalizumab treatment in asthma-COPD overlap syndrome. *J Asthma*. 2016;53(10):1048–1050.
35. Yalcin AD, Celik B, Yalcin AN. Omalizumab (anti-IgE) therapy in the asthma-COPD overlap syndrome (ACOS) and its effects on circulating cytokine levels. *Immunopharmacol Immunotoxicol*. 2016;38(3):253–256.
36. Criner GJ, Celli BR, Brightling CE, et al. Benralizumab for the prevention of COPD exacerbations. *N Engl J Med*. 2019;381(11):1023–1034.
37. Agache I, Akdis CA, Akdis M, et al. EAACI Biologicals Guidelines—recommendations for severe asthma. *Allergy*. 2021;76(1):14–44.
38. Pepper AN, Hanania NA, Humbert M, Casale TB. How to assess effectiveness of biologics for asthma and what steps to take when there is not benefit. *J Allergy Clin Immunol Pract*. 2021;9(3):1081–1088.
39. Pérez de Llano LA, Cosío BG, Domingo C, et al. Efficacy and safety of reslizumab in patients with severe asthma with inadequate response to omalizumab: a multicenter, open-label pilot study. *J Allergy Clin Immunol Pract*. 2019;7(7):2277–2283.e2.
40. Allakhverdi Z, Comeau MR, Jessup HK, et al. Thymic stromal lymphopoietin is released by human epithelial cells in response to microbes, trauma, or inflammation and potently activates mast cells. *J Exp Med*. 2007;204(2):253–258.
41. Ying S, O'Connor B, Ratoff J, et al. Thymic stromal lymphopoietin expression is increased in asthmatic airways and correlates with expression of Th2-attracting chemokines and disease severity. *J Immunol*. 2005;174(12):8183–8190.
42. Corren J, Parnes JR, Wang L, et al. Tezepelumab in adults with uncontrolled asthma. *N Engl J Med*. 2017;377(10):936–946.
43. Menzies-Gow A, Corren J, Bourdin A, et al. Tezepelumab in adults and adolescents with severe, uncontrolled asthma. *N Engl J Med*. 2021;384(19):1800–1809.
44. Kelsen SG, Agache IO, Soong W, et al. Astegolimab (anti-ST2) efficacy and safety in adults with severe asthma: a randomized clinical trial. *J Allergy Clin Immunol*. 2021;148(3):790–798.
45. Guntern P, Eggel A. Past, present, and future of anti-IgE biologics. *Allergy*. 2020;75(10):2491–2502.
46. Maurer M, Giménez-Arnau AM, Sussman G, et al. Ligelizumab for chronic spontaneous urticaria. *N Engl J Med*. 2019;381(14):1321–1332.
47. Lee JK, Simpson RS. Dupilumab as a novel therapy for difficult to treat chronic spontaneous urticaria. *J Allergy Clin Immunol Pract*. 2018;7(5):1659–1661.e1.
48. Maurer M, Khan DA, Elieh D, Komi A, Kaplan AP. Biologics for the use in chronic spontaneous urticaria: when and which. *J Allergy Clin Immunol Pract*. 2022;9(3):1067–1078.
49. Altrichter S, Staubach P, Pasha M, et al. Efficacy and safety data of AK002, an anti-Siglec-8 monoclonal antibody. *Patients With Multiple Forms of Uncontrolled Chronic Urticaria (CU): Results From an Open-Label Phase 2a Study*. 2019. Presented at the:.
50. Bachert C, Han JK, Desrosiers M, et al. Efficacy and safety of dupilumab in patients with severe chronic rhinosinusitis with nasal polyps (Liberty NP SINUS-24 and Liberty NP SINUS-52): results from two multicentre, randomised, double-blind, placebo-controlled, parallel-group phase 3 trials. *Lancet*. 2019;394(10209):1638–1650.
51. Gevaert P, Omachi TA, Corren J, et al. Efficacy and safety of omalizumab in nasal polyposis: 2 randomized phase 3 trials. *J Allergy Clin Immunol*. 2020;146(3):595–605.
52. Bagnasco D, Brussino L, Bonavia M, et al. Efficacy of Benralizumab in severe asthma in real life and focus on nasal polyposis [e-pub ahead of print]. *Respir Med*. doi:10.1016/j.rmed.2020.1060802020, accessed October 6, 2021.
53. Gevaert P, Calus L, Van Zele T, et al. Omalizumab is effective in allergic and nonallergic patients with nasal polyps and asthma. *J Allergy Clin Immunol*. 2013;131(1):110–116.e1.
54. Prætorius K, Henriksen DP, Schmid JM, et al. Indirect comparison of efficacy of dupilumab versus mepolizumab and omalizumab for severe type 2 asthma. *Eur R J Open Res*. 2021;7(3):00306–02021.
55. Peters AT, Han JK, Hellings P, et al. Indirect treatment comparison of biologics in chronic rhinosinusitis with nasal polyps. *J Allergy Clin Immunol Pract*. 2021;9(6):2461–2471.e5.
56. Wollenberg A, Blauvelt A, Guttman-Yassky E, et al. Tralokinumab for moderate-to-severe atopic dermatitis: results from two 52-week, randomized, double-blind, multicentre, placebo-controlled phase III trials (ECZTRA 1 and ECZTRA 2). *Br J Dermatol*. 2021;184(3):437–449.
57. Guttman-Yassky E, Blauvelt A, Eichenfield LF, et al. Efficacy and safety of lebrikizumab, a high-affinity interleukin 13 inhibitor, in adults with moderate to severe atopic dermatitis: a phase 2b randomized clinical trial. *JAMA Dermatol*. 2020;156(4):411–420.
58. Simpson EL, Parnes JR, She D, et al. Tezepelumab, an anti-thymic stromal lymphopoietin monoclonal antibody, in the treatment of moderate to severe atopic dermatitis: a randomized phase 2a clinical trial. *J Am Acad Dermatol*. 2018;80(4):1013–1021.
59. Guttman-yassky E, Brunner PM, Neumann AU, et al. Efficacy and safety of fezakinumab (an IL-22 monoclonal antibody) in adults with moderate-to-severe atopic dermatitis inadequately controlled by conventional treatments: a randomized, double-blind, phase 2a trial. *J Am Acad Dermatol*. 2018;78(5):872–881.e6.
60. Silverberg JI, Pinter A, Pulka G, et al. Phase 2B randomized study of nemolizumab in adults with moderate-to-severe atopic dermatitis and severe pruritus. *J Allergy Clin Immunol*. 2020;145(1):173–182.
61. Kabashima K, Matsumura T, Komazaki H, Kawashima M. Nemolizumab-JP01 Study Group. Trial of Nemolizumab and topical agents for atopic dermatitis with pruritus. *N Engl J Med*. 2020;383(2):141–150.
62. Fiocchi A, Artesani MC, Riccardi C, et al. Impact of omalizumab on food allergy in patients treated for asthma: a real-life study. *J Allergy Clin Immunol Pract*. 2019;7(6):1901–1909.e5.
63. Sampson HA, Leung DY, Burks AW, et al. A phase II, randomized, doubleblind, parallel-group, placebocontrolled oral food challenge trial of Xolair (omalizumab) in peanut allergy. *J Allergy Clin Immunol*. 2011;127(5):1309–1310.e1.
64. Savage JH, Courneya J-P, Sterba PM, Macglashan DW, Saini SS, Wood RA. Kinetics of mast cell, basophil, and oral food challenge responses in omalizumab-treated adults with peanut allergy. *J Allergy Clin Immunol*. 2012;130(5):1123–1129.e2.
65. Brandström J, Vetander M, Lilja G, et al. Individually dosed omalizumab: an effective treatment for severe peanut allergy. *Clin Exp Allergy*. 2017;47(4):540–550.
66. Wood RA, Kim JS, Lindblad R, et al. A randomized, double-blind, placebo-controlled study of omalizumab combined with oral immunotherapy for the treatment of cow's milk allergy. *J Allergy Clin Immunol*. 2016;137(4):1103–1110.e11.
67. MacGinnitie AJ, Rachid R, Gragg H, et al. Omalizumab facilitates rapid oral desensitization for peanut allergy. *J Allergy Clin Immunol*. 2017;139(3):873–881.e8.
68. Andorf S, Purington N, Block WM, et al. Anti-IgE treatment with oral immunotherapy in multifood allergic participants: a double-blind, randomised, controlled trial. *Lancet Gastroenterol Hepatol*. 2018;3(2):85–94.
69. Chinthrajah S, Cao S, Liu C, et al. Phase 2a randomized, placebo-controlled study of anti-IL-33 in peanut allergy. *JCI Insight*. 2019;4:(22) e131347.
70. Rocha R, Vitor AB, Trindade E, et al. Omalizumab in the treatment of eosinophilic esophagitis and food allergy. *Eur J Pediatr*. 2011;170(11):1471–1474.
71. Hirano I, Dellon ES, Hamilton JD, et al. Efficacy of dupilumab in a Phase 2 randomized trial of adults with active eosinophilic esophagitis. *Gastroenterology*. 2020;158(1):111–122.e10.
72. Dellon ES, Peterson KA, Murray JA, et al. Anti–Siglec-8 antibody for eosinophilic gastritis and duodenitis. *N Engl J Med*. 2020;383(17):1624–1634.
73. Kuang FL, Alao H, Kumar S, et al. Benralizumab (anti-IL5Rα) depletes gut tissue eosinophilia and improves symptoms in hypereosinophilic syndrome with gastrointestinal involvement. *J Allergy Clin Immunol*. 2018;141(2):AB196.
74. Assa'ad AH, Gupta SK, Collins MH, et al. An antibody against IL-5 reduces numbers of esophageal intraepithelial eosinophils in children with eosinophilic esophagitis. *Gastroenterology*. 2011;141(5):1593–1604.
75. Straumann A, Conus S, Grzonka P, et al. Anti-interleukin-5 antibody treatment (mepolizumab) in active eosinophilic oesophagitis: a randomised, placebo-controlled, double-blind trial. *Gut*. 2010;59(1):21–30.
76. Spergel JM, Rothenberg ME, Collins MH, et al. Reslizumab in children and adolescents with eosinophilic esophagitis: results of a double-blind, randomized, placebo-controlled trial. *J Allergy Clin Immunol*. 2012;129(2):456–463. 463.e1-463.e3.
77. Rothenberg ME, Wen T, Greenberg A, et al. Intravenous anti-IL-13 mAb QAX576 for the treatment of eosinophilic esophagitis. *J Allergy Clin Immunol*. 2015;135(2):500–507.
78. Hirano I, Collins MH, Assouline-Dayan Y, et al. RPC4046, a monoclonal antibody against IL13, reduces histologic and endoscopic activity in patients with eosinophilic esophagitis. *Gastroenterology*. 2019;156(3):592–603.e10.