

Strategies for Choosing a Biologic for Your Allergy or Asthma Patient

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Title: Strategies for Choosing a Biologic for Your Allergy or Asthma Patient

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Abbreviations/Acronyms:

ABPA: Allergic Bronchopulmonary Aspergillosis

ACOS: Asthma-Chronic Obstructive Pulmonary Disease Overlap Syndrome

ACT: Asthma Control Test

BMI: Body Mass Index

CAPS: Cryopyrin-Associated Periodic Syndromes

CIU: Chronic Idiopathic Urticaria

CRSwNP: Chronic Rhinosinusitis with Nasal Polyposis

CSU: Chronic Spontaneous Urticaria

EGPA: Eosinophilic Granulomatosis with Polyangiitis

EoE: Eosinophilic Esophagitis

FcεRI: High Affinity IgE Receptor

FDA: Food and Drug Administration

FeNO: Fractional Exhaled Nitric Oxide

HES: Hypereosinophilic Syndrome

ICS: Inhaled Corticosteroid

IgE: Immunoglobulin E

IL: Interleukin

IV: Intravenous

kg: Kilogram

mg: Milligram

mRNA: Messenger Ribonucleic Acid

OCS: Oral Corticosteroid

OIT: Oral Immunotherapy

SC: Subcutaneous

T2: Type-2

TSLP: Thymic Stromal Lymphopoietin

Abstract

Objective To summarize the therapeutic effects and safety of biologics either approved or in clinical development for asthma, COPD, urticaria, nasal polyps, atopic dermatitis, and eosinophilic esophagitis. This review attempts to provide some guidance when choosing between agents.

Data Sources Recent published papers obtained through PubMed database searches, including research articles, review articles, and case reports.

Study Selections PubMed database searches were conducted using the keywords: biologics, asthma, COPD, urticaria, atopic dermatitis, food allergy, nasal polyps, eosinophilic esophagitis. **Results** The approval of omalizumab by the FDA in 2003 for asthmatics paved the way for development of multiple biologics for a variety of respiratory and allergic diseases. FDA approved agents include mepolizumab, reslizumab, benralizumab and dupilumab, and several more are in late stages of clinical development. Due to overlap in pathogenesis of respiratory and allergic diseases, many of these biologics target multiple respiratory and allergic diseases simultaneously.

Conclusion The numerous biologic options have made selecting 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. Nonetheless, 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 about 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 three

years our previous review article in the Annals on this subject was published¹, new agents and indications for existing agents have exploded onto the scene (Figure 1). Now more than ever, figuring out which biologic to choose can be a tricky process. The goal of this review is to build upon the previous paper, and to provide further clinical situations where one biologic may be preferred over another.

Asthma

Severe asthma is defined as asthma that is treated with a high dose inhaled corticosteroid (ICS) and an additional controller medication and/or systemic corticosteroids², 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. T2 high suggests the presence of Th2 CD4+ lymphocytes that characteristically secrete interleukin (IL) 4, 5, 9 and 13³. These cytokines cause airway inflammation and remodeling in the epithelium and subepithelial matrix³. 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 to controller therapy that does not distinguish between asthma phenotypes. Variation in clinical response to therapy can be linked to genetic, pharmacologic, physiologic and immunologic differences⁴. 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 United States Food and Drug Administration (FDA) currently has approved five biologics for the treatment of patients with severe asthma. The pivotal studies for the four 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 eosinophils $\geq 1\%$, blood eosinophil ≥ 150 cells/ μL or a fractional exhaled nitric

oxide (FeNO) ≥ 20 ppb, but other thresholds have been proposed in this contentious debate. Patients with allergic asthma have worsening symptoms when exposed to aeroallergens, and their serum immunoglobulin E (IgE) usually exceeds 30 IU/mL.

Omalizumab

The first biologic approved by the FDA for use in patients with moderate to severe persistent allergic asthma was omalizumab (XOLAIR®) in June of 2003. Omalizumab is a monoclonal antibody that targets IgE, which prevents its binding to the high affinity IgE receptor (FcεRI) on basophils, mast cells and dendritic cells. The lack of engagement by IgE causes downregulation of FcεRI 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 cells⁵. 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 to placebo⁶. In the subset of patients with peripheral eosinophils $\geq 400/\mu\text{L}$, reductions in asthma exacerbations was reported to be 74%⁷. In contrast to eosinophil counts, neither baseline IgE levels nor the number and type of allergen sensitizations predict likelihood of response⁸. In an open-label pragmatic trial, omalizumab led to a 39% reduction in daily oral corticosteroid use over 52 weeks, and a statistically significant improvement in quality-of-life questionnaires when compared to responses one year prior⁸. 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 (ACT) achieved good asthma control (ACT ≥ 20) after 12 months of using omalizumab⁹. Comorbid conditions that favor use of omalizumab include CRSwNP, chronic urticaria (both FDA approved indications), allergic rhinitis¹⁰, food allergies¹¹, allergic bronchopulmonary aspergillosis (ABPA), eosinophilic granulomatosis with polyangiitis (EGPA)¹² and asthma-COPD (chronic obstructive pulmonary disease) overlap syndrome (ACOS)¹³. Omalizumab is

approved for asthma in children 6 and above. The recommended subcutaneous dose is administered either in a healthcare setting or at home every 2 or 4 weeks depending on body weight and IgE levels¹⁴.

Mepolizumab

Omalizumab was on the market for over ten years before the next biologic became FDA approved. In November of 2015, mepolizumab (NUCALA®) was FDA approved for use as an add-on maintenance treatment for patients with severe eosinophilic asthma aged 6 years and older¹⁵. Mepolizumab is an IgG1 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 EGPA,¹⁵ hypereosinophilic syndrome, and chronic rhinosinusitis with nasal polypsis¹⁸. Mepolizumab has also demonstrated positive effects in ABPA¹⁹ and eosinophilic COPD²⁰. Mepolizumab is approved for children ages 6 years and older. It is dosed as 100 mg subcutaneous injection for patients ≥ 12 years old and as 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 clinic.

Reslizumab

Soon after mepolizumab was FDA approved, reslizumab (CINQAIR®) 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 IL5 but is an IgG4-kappa molecule. Reslizumab was shown to reduce the frequency of asthma exacerbations at 1 year in a phase III pooled data analysis by 54% compared to placebo when blood eosinophil levels were ≥ 400 cells/ μ L²¹. Reslizumab significantly reduces blood eosinophil counts. Elevated pretreatment blood eosinophil

counts predict greater improvements in lung function and asthma control²². Its weight-based dosing may help patients with higher body mass index (BMI). In prednisone-dependent severe asthma patients, weight-adjusted reslizumab was superior to fixed dose mepolizumab in achieving asthma control²³. Reslizumab may also be efficacious in CRSwNP²⁴. It is administered as a 3 mg/kg infusion once every 4 weeks over 20 to 50 minutes²⁵.

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 development of naïve Th cells to Th2 cells. IL-13 has many important roles in asthma pathogenesis including mucus production and airway hyperresponsiveness. In March of 2017, dupilumab (DUPIXENT®) was FDA-approved for use in patients with eosinophilic or oral corticosteroid-dependent (regardless of eosinophil counts) moderate-to-severe asthma in patients ages 12 years or older²⁶. Dupilumab is an anti-IL-4 α receptor monoclonal antibody. Dupilumab was shown in the phase III LIBERTY ASTHMA QUEST trial to decrease severe asthma exacerbations in patients with moderate-to-severe asthma by 48% when compared to placebo with a significant improvement in forced expiratory volume in one second (FEV1) by 320 mL²⁷. 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 to placebo and approximately 50% were able to completely discontinue oral corticosteroid use²⁸. Elevated fractional exhaled nitric oxide (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 side 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 shown favorable outcomes in its use for aspirin-exacerbated respiratory diseases²⁹ and pediatric asthma patients younger than 12 years. In patients with eosinophilic moderate-to-severe asthma, the initial dose is a 400mg subcutaneous injection followed by 200mg pre-filled injection administered every two weeks. For patients with oral corticosteroid-dependent moderate to severe asthma, the recommended dose is an initial 600mg injection followed by 300mg pre-filled injection given every two weeks²⁶.

Benralizumab

Eight months following the approval of dupilumab in November of 2017, benralizumab (FASENRA®) became the most recently FDA approved biologic for asthma. It is approved for patients 12 years and older with severe eosinophilic asthma²⁹. Benralizumab is a monoclonal IgG1 kappa antibody against the IL-5 α receptor resulting in antibody-dependent cell-mediated cytotoxicity of cells expressing these receptors³⁰. 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 pre-bronchodilator FEV1 by 159mL^{31,32}. Benralizumab was also shown to significantly reduce oral corticosteroid use by $\geq 50\%$ in two-thirds of patients³³. It is administered as a 30mg subcutaneous injection every 4 weeks for the first 3 doses and then once every 8 weeks³⁰.

COPD and ACOS

Using monoclonal antibodies targeting the IL-4, -5 and -13 and IgE signaling pathways has become an area of interest in the possible treatment of Chronic Obstructive Pulmonary Disease (COPD) and asthma-COPD overlap syndrome (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 post-hoc

analysis found that patients who were treated with omalizumab had similar improvement in asthma outcomes if they met criteria for ACOS¹³. In a phase III trial of patients with COPD and eosinophils $\geq 150/\text{mL}$ ⁴ treated with mepolizumab 100mg subcutaneous injection every 4 weeks, there was an 18% decrease in annual rate of moderate or severe COPD exacerbations²⁰. Similar outcomes were not observed when patients with moderate to very severe COPD were studied in a phase 3 randomized clinical trial using benralizumab³⁶.

Which to choose?

Choosing the best biologic depends on the asthma phenotype, age, comorbidities, goals of therapy (e.g., dupilumab for oral corticosteroid reduction), triggers of exacerbations (e.g., omalizumab for virus and allergen-induced exacerbations) and side effect profile (Table 1). Only dupilumab and omalizumab are also indicated for patients with moderate persistent asthma, while the rest are exclusively indicated for those with severe disease. Omalizumab and mepolizumab are approved for patients ≥ 6 years old, benralizumab and dupilumab are approved for patients ≥ 12 years old and reslizumab is approved for adults 18 years and older. Omalizumab, mepolizumab and dupilumab can simultaneously help patients with moderate to severe asthma and chronic rhinosinusitis with nasal polyposis (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 oral corticosteroid dependence or improving asthma symptom control, may influence which biologic is chosen. Once a biologic is decided upon, it is recommended to closely monitor symptoms and overall asthma control over a 4-to-6-month interval³⁷. During follow up, patient related factors such as poor adherence to biologic or other asthma therapies and poorly controlled comorbidities should be optimized³⁷. 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 a suboptimal response defined as a less than 50% exacerbation reduction, minimal symptoms improvement, no reduction in daily OCS or lung function improvement³⁸. Patients with a suboptimal response after review of patient, disease and medication-related factors should be evaluated for treatment with a different biologic³⁹.

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, 5, 9 and 13), but for many patients with nonallergic or non-eosinophilic phenotypes, there is significant 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 significant improvements in patients classified as either T2 low or T2 high⁴². In a recent phase 3 trial, the use of tezepelumab was associated with an overall annual rate reduction of asthma exacerbations by 55.7% and by 39% in patients with eosinophil count at baseline < 150 cells/ μ L⁴³.

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 upregulation of TNF- α , IFN- γ , IL-5, IL-6, IL-9, and IL-13. Astegolimab is an IL-33 receptor inhibitor that targets ST2 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 to placebo, astegolimab 490mg subcutaneous every 4 weeks led to a 43% relative reduction in asthma exacerbation rate (AER) with a number needed to treat of 8.77. In a subgroup analysis of patients with eosinophils < 300 cells/ μ L, astegolimab 490mg had a 53.6% relative reduction in AER compared to placebo with a number needed to treat of 2.63⁴⁴. Astegolimab, like tezepelumab, may become an option in the future for patients with T2 low or T2 high asthma.

Due to the success of these biologics, blockers of other alarmins, new anti-IgE molecules, and longer-lasting IL-5 blockers are in clinical development⁴⁵. Hopefully, these advances will lead to better and more cost-effective therapies for patients with moderate to severe asthma of both T2hi and T2lo 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/CSU) is defined as recurrent episodes of hives and/ or angioedema for longer than 6 weeks. These symptoms can significantly affect patient's quality of life. First line therapy for CIU consists of high dose second generation antihistamines, however over 50% of patients do not respond or do not achieve an acceptable level of control of their symptoms. Other adjunct therapies, such as dapson, tacrolimus, and cyclosporin can have severe side effects, such

as bone marrow suppression or kidney injury; thus, it is preferable that their use be avoided. Biologic therapies provide an ideal treatment option with minimal side effects and excellent response rates¹. Anti-IgE therapy, anti-IL4/13 and anti-IL-1 therapy 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 Fc ϵ R1. Omalizumab and Ligelizumab can simultaneously inhibit both processes by triggering a significant reduction in serum IgE, leading to the subsequent induction of internalization of Fc ϵ R1 on mast cells and basophils¹.

Omalizumab's use in urticaria was thoroughly discussed in our previous review article¹, thus we will mainly focus on new insights. Omalizumab is currently FDA approved for patients 12 years old and older. More than 50% of patients experienced complete resolution of their hives with 300 mg SC every 4 weeks, and phase 3 trials showed significant improvement in quality-of-life scores. It has also been shown to help with co-existing angioedema. In patients with autoantibodies, the clinical effects can be delayed. Omalizumab has also been shown in smaller studies to be beneficial for patients with urticarial vasculitis and inducible urticarias¹.

Ligelizumab has an almost 40-fold higher affinity for IgE given its slower offloading time. It more potently inhibits IgE binding to Fc ϵ R1, 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 is 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 completed⁴⁶.

Dupilumab

Dupilumab indirectly lowers IgE levels, and thus triggers internalization of FcεR1, by blocking the IL-4α receptor and subsequent IL-4/13 signaling⁴⁷. This inhibits class switching of IgM to IgE. High serum levels of IL-4 and IL-13 have been reported in some CIU patients, while 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 point of care biomarkers to predict responsiveness are 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 (one did not report their urticaria status at the end of the study). Clinical trials exploring the utility of dupilumab for both CIU and chronic inducible urticaria are ongoing⁴⁷. A recent press release indicated that a phase 3 trial met its primary endpoints and all key secondary endpoints at 24 weeks, showing 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-naïve patients and omalizumab-resistant patients. It has also demonstrated 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 (CAPS) spectrum. The current FDA approved options are anakinra (recombinant human IL-1Ra antagonist), canakinumab (humanized anti-IL-1β monoclonal antibody), and rilonacept (soluble decoy receptor that blocks IL-1β

signaling). Trials have also shown favorable data for the use of anakinra and canakinumab in Schnitzler syndrome¹.

Other agents currently in development

Other monoclonal antibodies on the horizon for CIU include anti-IL-5 and anti-IL5R agents like mepolizumab and benralizumab respectively, tezepelumab, and the CD117 inhibitor celledex. All are in various stages of development, ranging from phase I to phase II trials⁴⁸.

Which to choose?

There are currently no commercially available biomarkers to accurately predict responsiveness to biologics for CIU, but low IgE levels have been correlated with favorable response to omalizumab. Since 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 co-existing idiopathic anaphylaxis or a possible mast cell disorder may benefit from omalizumab. Ligelizumab could be a good alternative agent for both 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 where intranasal glucocorticoid therapy is insufficient, recurrent oral glucocorticoid therapy, although effective, is not ideal given the plethora of potential side effects and long-term health complications. Elevated tissue eosinophilia in nasal polyp patients is also associated with a higher chance of recurrence after surgical removal. These patients have also been found to have elevated IL-4, 5 and 13 levels, as well as elevated mucosal IgE¹.

Dupilumab

Dupilumab is currently FDA approved for nasal polyp patients 18 years or older either as a pre- or post-surgical option. It requires a one-time 600 mg loading dose with subsequent 300 mg Q2 week dosing. No biomarkers are required for its use. In multiple studies it was shown to reduce polyp size, prevent the need for surgery, and had a corticosteroid sparing effect. It also led to significant improvement in symptom and quality of life scores. It is also effective in patients with co-existing Th2 asthma^{1,50}.

Omalizumab

Omalizumab is also FDA approved for nasal polyp patients 18 years or older. The biomarker used to guide therapy is an IgE level between 30 – 1,500 IU/mL. Unlike dupilumab, the dosing is weight based (mg/kg) and it is administered every 2 -4 weeks. Like dupilumab, it can be used as a pre- or post-surgical option. Omalizumab also showed a statistically significant reduction in the need for surgery, had a corticosteroid sparing effect (non-significant), and significantly decreased polyp size. Omalizumab did lead to improvement in symptom and quality of life scores. Omalizumab could be utilized in patients with co-existing Th2 asthma, particularly with an elevated IgE level⁵¹.

Mepolizumab and Benralizumab

Mepolizumab is now FDA approved and benralizumab is currently in phase 3 clinical trials for nasal polyposis. SYNAPSE¹⁸ was a randomized, double-blind, placebo-controlled, parallel-group, phase 3 trial of 100 mg mepolizumab subcutaneously or placebo once every 4 weeks, in addition to standard of care. Total endoscopic nasal polyp score significantly improved at week 52 from baseline with mepolizumab versus placebo and nasal obstruction during weeks 49–52 also significantly improved. Mepolizumab reduced 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 levels¹⁸.

In preliminary studies, benralizumab showed a reduction in polyp size and need for surgery, as well as a corticosteroid sparing effect. However, it is important to note that mepolizumab showed a benefit irrespective of co-morbid asthma or N-ERD, while benralizumab has only been evaluated in the setting of severe eosinophilic asthma, but phase 3 data are pending⁵².

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 showed 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 omalizumab⁵⁴. However, direct comparative studies between the biologics in the same patients are lacking but are planned. Choice of a specific biologic might also be influenced by comorbid conditions treated by the biologic⁵⁵.

Atopic Dermatitis

Atopic dermatitis is one of the more life-impairing and potentially disfiguring diseases allergists treat. Key cytokines involved in the 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-31¹.

Dupilumab

Dupilumab is currently the only biologic FDA approved for patients 6 years and older with atopic dermatitis. Studies are currently ongoing for children between 2 and 5 years of age. It requires a onetime loading dose of 600 mg SC, then 300 mg every two weeks thereafter. It does not require any biomarkers for approval. Its concomitant use with topical corticosteroids (TCS) lead to even greater

improvement in symptoms. It resulted in significant improvements in quality of life and symptom scores¹.

IL-13 blockers

There are many studies examining the therapeutic potential of monoclonal antibodies against IL-13 for atopic dermatitis. Tralokinumab demonstrated statistically significant improvements over placebo in 2 phase 3 clinical trials recently completed⁵⁶. The efficacy and safety of lebrikizumab in adults with moderate to severe atopic dermatitis was demonstrated in a phase 2b randomized clinical trial⁵⁷.

Tezepelumab

A phase 2a trial of tezepelumab, an anti-TSLP monoclonal antibody, in adults with moderate to severe atopic dermatitis showed some promising results. However, a second phase 2 trial for atopic dermatitis was discontinued due to a lack of efficacy⁵⁸.

Fezakinumab

Fezakinumab, an anti-IL22 agent, has been examined in Phase 2a clinical trials for atopic dermatitis. One drawback of this therapy is that it currently is only available as an IV 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 scores⁵⁹.

Nemolizumab

Nemolizumab blocks anti-IL-31R α and is currently being examined as a possible atopic dermatitis therapy. Its dosing is 60 mg SC every 4 weeks. It led to improvement in pruritus (primary endpoint) 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 only and the best option.

Food Allergy

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

Omalizumab and Ligelizumab

There have been at least three peanut studies and one multi-food non-OIT study examining omalizumab's ability to allow patients to have a higher threshold for reactivity to the offending food⁶²⁻⁶⁸. The peanut studies showed an increase in the tolerated peanut dose, but one was terminated early due to two severe reactions during the entry food challenges. However, the increases in doses tolerated were substantial, with one study showing an increase from 80 mg to 10,000 mg (approximately 35 peanut kernels) at week 24. The multi-food data showed similar results with one study⁶² demonstrating a greater than eight-fold increase in tolerated milk, egg, wheat and hazelnut in the omalizumab versus placebo group. 70% of subjects were able to complete an oral food challenge dose of >7,000 mg and able to reintroduce the food into their diet without OIT. The OUTMATCH study funded by NIH is currently enrolling. This study is examining whether omalizumab as monotherapy is as good or better than omalizumab plus OIT. Since the previous studies with omalizumab were often not double-blind, randomized controlled studies in large cohorts, the OUTMATCH trial will be important in determining the utility of omalizumab as monotherapy or in conjunction with OIT⁶²⁻⁶⁸.

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

Dupilumab

There are no published data available for dupilumab and food allergy, but there are currently several studies underway examining its effectiveness (clinical trial IDs: NCT03682770, NCT03793608, NCT04148352, NCT04462055, NCT03679676). Most are to examine if the dose threshold eliciting symptoms is increased, but one exciting study is looking at whether dupilumab in multi-food allergic patients with atopic dermatitis have an increase in eliciting dose after 28 weeks (clinical trial ID: NCT04462055). There are currently two multi-food studies underway (clinical trial IDs: NCT04462055, NCT03679676) and one peanut study (clinical trial ID: NCT03682770). As for food OIT-dupilumab studies, there are currently two studies underway, one 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-IL33 monoclonal that was examined in 20 peanut allergic patients (5 placebo and 15 verum). After a single dose, an impressive 73% passed a 275 mg challenge on day 15 vs 0% on day one. 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 15⁶⁹.

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 upon the outcome of studies

examining 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 suffering from food allergy, the healthcare 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-IL5 and anti-IL5R α . However, data from previous trials have not been very promising. Nevertheless, there are several agents being examined for EoE at this time.

Omalizumab

Omalizumab's foray into EoE was unfortunately not very impressive. It showed no reduction in eosinophils on repeat biopsy, and only lead to mild improvement in symptom and quality of life scores⁷⁰.

Dupilumab

Dupilumab was examined 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 statistically significant reduction in eosinophil levels and improvement in symptom and quality of life scores⁷¹. 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 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 scores⁷².

Mepolizumab, Reslizumab, Benralizumab

All three of the IL-5 blockers are currently being studied as potential EoE therapies, except for benralizumab which was studied in patients with hypereosinophilic syndrome (HES), 7 of whom had gastrointestinal involvement⁷³. However, two of the agents, mepolizumab and reslizumab, were studied as IV options. All three lead to expected reduction in tissue eosinophil levels, and reslizumab lead to statistically significant improvement in symptom and quality of life scores (this was not examined in the mepolizumab and benralizumab studies)^{73–76}.

Dectrekumab and RPC4046

Dectrekumab (IV agent) and RPC4046 are two new anti-IL-13 agents currently being studied for use in EoE. Both lead to reduction in tissue eosinophil numbers. Symptom and quality of life scores were not examined for Dectrekumab, but they were for RPC4046, which demonstrated improvement in these scores^{77,78}.

Other agents:

Anti-IL-15 and anti-TNF alpha are two other classes of agents being explored for the treatment of EoE, but there are no published data currently.

Which to choose?

It is too early to recommend a biologic agent for EoE, but dupilumab and reslizumab appear 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 examined for EoE are IV preparations, which may limit their use. Benralizumab and liletelimab directly lead to

eosinophil apoptosis, which is appealing, and limits the chance for rebound in eosinophils that can occur with agents mainly targeting eosinophil recruitment.

Conclusions

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 significant benefit. However, there needs to be more studies examining the cost-effectiveness of these therapies, appropriate candidates for these therapies and selective biomarkers to better predict responsiveness to these therapies. 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 be used only for appropriately selected patients. Furthermore, since none of these agents have shown the ability to cure these diseases, we need to understand how best to determine a course of therapy regarding dosing, corticosteroid sparing effects, duration of therapy and when and how to restart or switch biologics.

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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/o	N/A (studies ≥ 12 y/o)	N/A (youngest in case series was 18 y/o)	N/A (youngest in case series was 18 y/o)
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-IL4/13Ra - Case series examined 6 patients who failed omalizumab - All 5 out of 6 (one did not report urticaria status) responded with dupilumab	Siglec-8 Inhibitor
Route	SC	SC	SC	SC
Frequency	Every 2 - 4 weeks	Every 4 weeks	Every 2 weeks	Every 4 weeks
Dose	150 - 300 mg	240 mg	600mg loading dose, 300mg 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 naïve and omalizumab non-responsive patients)

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/o	≥ 18 y/o	N/A (studies ≥ 18 y/o)	N/A
Mechanism of Action	Anti-IL4/13Ra	Anti-IgE	Anti-IL5	Anti-IL5Ra
Route	SC	SC	IV or SC	SC
Frequency	Every 2 weeks	Every 2 - 4 weeks	Every 4 weeks	Every 4 weeks for the first 3 doses, every 8 weeks 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 cut-off was used for enrollment in one, ≥ 300 in another)
Reduction in Polyp Size	Yes	Yes	Yes (irrespective of co-morbid asthma or N-ERD)	Yes - Note: studies were done in the context of co-existing severe eosinophilic asthma
Reduction in Need for Surgery	Yes	Not statistically significant decrease	Yes	Yes
Steroid sparing effect	Yes	Not statistically significant	Yes	Yes

Table 3: Comparisons Among Biologic Therapies for Atopic Dermatitis

		decrease		
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 week 24	Yes (SNOT-22, UPSIT, and TNSS)	Yes (SNOT-22, VAS)	Yes (SNOT-22, NRS, endoscopic nasal polyp score, Lund-Mackay CT score)

Variable	Dupiluma b ¹	Tezepelu mab ⁵⁸	Fezakinu mab ⁵⁹	Nemolizum ab ^{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/o	N/A	N/A (>= 18 y/o studies)	N/A	N/A	N/A
Mechanism of Action	Anti-IL4/13Ra	Anti-TSLP	Anti-IL22	Anti-IL31Ra	Anti-IL13	Anti-IL13
Route	SC	SC	IV	SC	SC	SC
Frequency	Every 2 weeks	Every 2 weeks	Every 2 weeks	Every 4 weeks	Every 2 weeks	Every 2 - 4 weeks
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 loading dose [LD]), 250 mg every 4 weeks (500-mg LD), or 250 mg every 2 weeks (500-mg LD at baseline and week 2)
Biomarkers	None	N/A	N/A	N/A	N/A	N/A
Steroid sparing effect	N/A (but addition of TCS lead to even more improvement)	N/A (but 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 addition of TCS lead to even more improvement)	Yes (most did not need rescue medication, including topical steroids, by week 16)	Yes (three times less usage than placebo group)

Symptom Score and Quality of life						
Improvements vs placebo (statistically significant)	Yes (EASI and extent of BSA involvement)	Yes (EASI50 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 puritis)

Table 4: Comparisons Among Biologic Therapies for Food Allergy

Variable	Omalizumab ⁶²⁻⁶⁸	Dupilumab (no published data, see text for clinical trial IDs)	Etokimab ⁶⁹
FDA approval status	No	No	No
Age approved	N/A (8 - 44 y/o)	N/A	N/A
Mechanism of Action	Anti-IgE	Anti-IL-4/13Ra	Anti-IL33
Route	SC	SC	N/A
Frequency	Every 2 - 4 weeks	N/A	N/A (after 1 single injection)
Dose	N/A	N/A	N/A
Biomarkers	N/A (Flocchi Total IgE 208 - 1491)	N/A	N/A

Amount of target food able to ingest	Various Studies: - Sampson et al⁵⁶ (peanut): Increase threshold dose vs baseline, but study terminated due to 2 severe reactions during entry DBPCFC - Savage⁵⁷ (peanut): Increased median tolerated dose from 80 mg to 6,500 mg @ week 5, 4 tolerated full 10,000 mg @ week 24 - Brandstrom⁵⁸ (peanut): 65% able to tolerate full dose (2,800 mg), all ingested at least 840 mg - Fiocchi⁵⁵ (multi-food allergic/single if failed OIT): mean increase in threshold from 1013 mg to 8728 mg (milk, egg, wheat, hazelnut), 70% tolerated complete OFC dose and able to reintroduce into diet without OIT * OUtMATCH Study Pending	Studies in the works: - Dupilumab monotherapy in peanut allergic patients: recruiting, goal = pass a low dose DBPCFC - Dupilumab multi-food allergic patients (vs omalizumab): recruiting; goal = passing 1043 mg DBPCFC at the end of week 44 - Dupilumab + multi-food allergic atopic dermatitis patients: recruiting, goal = change in eliciting dose after 28 weeks	Results after a single dose (peanut): - 73% passed CTD 275mg on day 15 vs 0% @ baseline (P=0.008), 57% on day 45 vs 0% @ baseline (placebo stayed at 0% for both) - 47% passed CTD 375 mg on day 15 vs 0% @ baseline, 29% on day 45 vs 0% @ baseline (placebo stayed at 0% for both) - One patient was able to tolerate ~ 500 mg on day 15
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Outcomes in Conjunction with OIT	Various Studies: - Wood⁵⁹ (milk): 88.9% vs 71.4% (placebo) passed 10 gm desensitization OFC @ month 28 (P=0.18); @ month 32 (16 weeks off OMA and 8 weeks of OIT), 48.1% vs 35.7% (placebo) had SU (P=0.42); 2.1% vs 16.1% (placebo) had symptoms during escalation (P<0.001); dose reactions needing treatment 0.0% vs 3.8% (placebo, P<0.001) - MacGinnitie⁶⁰ (peanut): 79.3% vs 12.5% (placebo) tolerated 2000 mg 6 weeks off omalizumab (P<0.001); 75.9% vs 1.5% (placebo) tolerated 4000 mg off omalizumab (P<0.001); reaction rates not significantly different, but omalizumab patients were exposed to higher peanut doses - Andorf⁶¹ (multi-food): 83% vs 33% (placebo) tolerated 2 gm of >= 2 foods @ 36 weeks (P=-.0044); 27% vs 68% (placebo) median per-subject percentage of OIT doses associated w/ adverse events (P=0.0082) * OUtMATCH Study Pending	Studies in the works: - Dupilumab in conjunction with peanut OIT: active but not recruiting, goal = pass 2044 mg DBPCFC at week 28 - Dupilumab in conjunction with milk OIT: not yet recruiting, goal = pass 2040 mg DBPCFC at week 18	N/A
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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-IL4/13Ra	Anti-Siglec-8	Anti-IL5	Anti-IL5	Anti-IL5Ra	Anti-IL13	Anti-IL13
Route	SC	SC	N/A	IV	IV	SC	IV	N/A
Frequency	Every 4 weeks	Weekly	N/A	N/A	N/A	Every 4 weeks	N/A	N/A

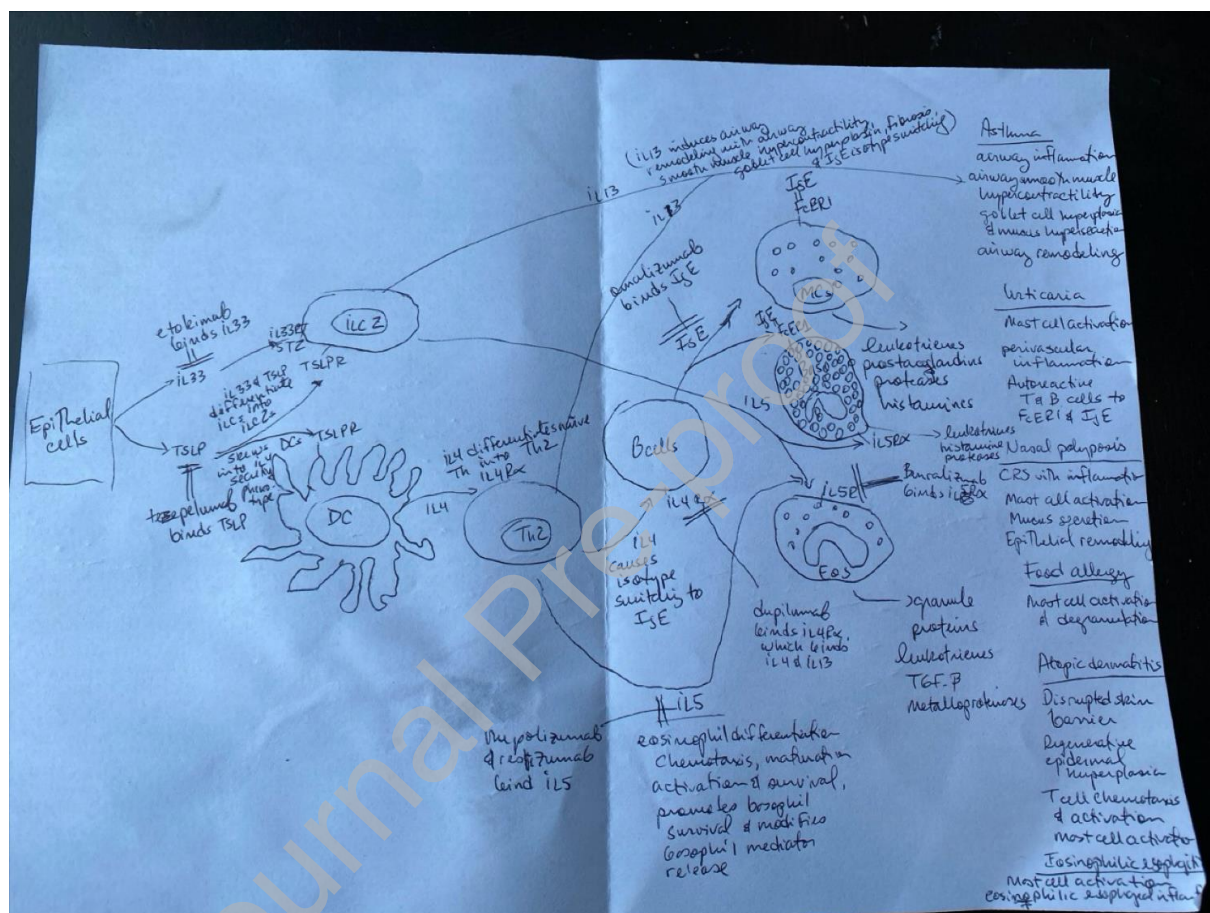
Dose	N/A	300 mg	N/A	750 mg x 2 doses -> 1,500 mg x 2 doses 0.55, 2.5, 10 mg/kg	1, 2 or 3 mg/kg	30 mg	N/A	N/A
Biomarkers	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 15	Esophageal eosinophils > 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=0.001)	N/A	Yes	N/A	N/A	No (high dose P=0.001)

Table 6: Comparison of Biologic Therapies for Asthma¹

Variable	Omalizumab	Mepolizumab	Reslizumab	Dupilumab	Benralizumab
FDA approval status	Yes	Yes	Yes	Yes	Yes
Age approved	≥ 6 years old	≥ 6 years old	≥ 18 years old	≥ 12 years old	≥ 12 years old
Mechanism of Action	Anti-IgE	Anti-IL5	Anti-IL5	Anti-IL4/13Ra	Anti-IL5Ra

Route	SC	SC	IV	SC	SC
Frequency	Every 2 to 4 weeks (weight based and pretreatment IgE)	Every 4 weeks	Every 4 weeks	Every 2 weeks	Every 4 weeks for 3 doses and then every 8 weeks
Dose	150 to 375 mg	40 to 100mg (based on age)	3 mg/kg infusion	400 to 600 mg initial dose followed by 200 - 300mg	30mg
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

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; **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; **Th2**: T helper 2; **TSLP**: thymic stromal lymphopoietin.



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 IL-13 blockers, tezepelumab, fezakinumab, and nemolizumab.
- There are currently no biologics FDA approved for the treatment of food allergy. Possible future therapies include omalizumab, Ligelizumab, dupilumab, and etokimab.
- There are currently no biologics FDA approved for the treatment of eosinophilic esophagitis. Possible future therapies include dupilumab, lirentelimab, mepolizumab, reslizumab, benralizumab, IL-13 blocking agents, anti-IL15 agents and anti-TNF alpha agents.