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REVIEW

The evolving landscape of immunotherapy for the treatment of allergic conditions

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Abstract

Allergic conditions, such as asthma, chronic urticaria, atopic dermatitis (AD), and eosinophilic esophagitis, have long been treated with oral and topical steroids which resulted in negative off-target effects. However, newer biologic medications are increasingly being developed and approved for treatment of these conditions. These medications have a variety of mechanisms of action to target pathophysiology specific to these diseases. As biologics become more targeted, fewer off-target effects are seen improving tolerability for patients as well as expanded options for treatment of these conditions. This review discusses monoclonal antibody therapies (omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab, tezepelumab, and tralokinumab) including their safety and use in asthma, chronic urticaria, AD, and eosinophilic esophagitis.

INTRODUCTION

The available treatments for managing allergic conditions have significantly evolved with the development of monoclonal antibodies (mAbs). These therapies target involved cytokines and immunologic pathways driving allergic disease pathophysiology (Table 1). Prior to the development of biologic therapies, patients with uncontrolled allergic disease, such as allergic asthma, chronic urticaria (CU), and atopic dermatitis (AD), often required treatment with systemic immunosuppression, which can lead to adverse effects (e.g., weight gain, osteoporosis, and mood changes). mAb therapies allow targeting specificity of the T-helper 2 (Th2) pathway involved in atopic disease rather than impacting immunologic pathways broadly. These therapies have demonstrated improved efficacy while avoiding systemic side effects caused by other therapies. This review will discuss allergic conditions that have currently US Food and Drug Administration (FDA) approved mAb therapies (asthma, CU, AD, and eosinophilic esophagitis). We will begin by discussing the mechanism of action for each mAb in use for these conditions and its safety data, followed by a description of key clinical studies for each mAb's use in a particular condition.

AVAILABLE MABS FOR ALLERGIC DISEASES

Omalizumab

Omalizumab, a humanized mAb, binds to IgE constant Cε3 region, preventing binding of IgE to the Fc-epsilon-RI receptor (FcεRI) and reducing the level of circulating IgE. This blockade prevents the release of inflammatory mediators, such as histamine, prostaglandins, and cysteinyl-leukotrienes (Figure 1). Receptor binding decreases FcεRI expression on basophils, mast cells, and dendritic cells which subsequently leads to a reduction in allergen presentation to T cells and an overall decrease in Th2-mediated allergic pathway activity.[1]

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TABLE 1 Characteristics for each biologic discussed.

Biologic	Mechanism of action	Indications	Age	Route	Dosing schedule	Efficacy	Pharmacokinetics	Potential adverse effects
Omalizumab	Binds to IgE constant Cε3 region, preventing binding of IgE to the FcεRI and reducing the level of circulating IgE	Allergic asthma Chronic urticaria	≥6 years ≥12 years	s.q.	Asthma: 75–375 mg q2-4 weeks, based on age, weight, IgE level Chronic Urticaria: 150–300 mg q4 weeks	Asthma[a]: 25–50% reduction in exacerbations, variable but minimal increase in FEV1 Chronic Urticaria[b]: ISS 8.6 reduction UAS7 19 reduction	Distribution: 78 ± 32 mL/kg[c] Bioavailability: 62% Half-life elimination: 26 days for asthma, 24 days for chronic urticaria	Black box warning for anaphylaxis, small risk of cardiovascular and cerebrovascular events
Mepolizumab	Binds to IL-5, preventing it from binding to its receptor (immunoglobulin G1 kappa 8)	Eosinophilic asthma	≥6 years	s.q.	Asthma: 40 mg q4 weeks in ages 6–11, 100 mg q4 weeks in ages 12 and older	Asthma[d]: 47–52% decrease in asthma exacerbations FEV1 increase of 210 mL 50% reduction in glucocorticoid dose	Distribution: 3.6 L[e] Bioavailability: 80% Half-life elimination: 16–22 days	Respiratory tract infection, headache, worsening asthma, bronchitis, zoster infection
Reslizumab	Neutralizes circulating IL-5 by preventing binding to the alpha chain of the IL-5 receptor complex	Eosinophilic asthma	≥18 years	IV	3 mg/kg q4 weeks	Asthma[f]: 50–59% decrease in exacerbation rate FEV1 increase 90-126 mL	Distribution: 5 L[g] Bioavailability: Unknown Half-life elimination: 24 days	Black box warning for anaphylaxis, nasopharyngitis
Dupilumab	Blocks both IL-4 and IL-13 signaling	Eosinophilic asthma Atopic dermatitis, moderate to severe Eosinophilic esophagitis	≥6 years ≥6 months ≥12 years	s.q.	Asthma: Loading dose: 400–600 mg based on age, OCS use, and co-morbid conditions. No loading dose <12 years old Maintenance dose: 100–300 mg q2-4 weeks based on age and weight AD: 200–300 mg q4 weeks based on weight EOE: 300 mg q every other week	Asthma[h]: 46–70% decrease in exacerbations FEV1 increase 130–140 mL 70.1% reduction in glucocorticoid dose AD[i]: 6 months– 6 years: 53% improvement in EASI 75 6 years – 11 years: 67.2–69.7% had >75% improvement in EASI score 12 years – 18 years: 64–65.9% had improvement in EASI 75 ≥ 18 years: 75% improvement in EASI score, 36% improvement in IGA score EOE[j]: 3.0 reduction in PRO score 82.6% achieved <15 EOS/HPF 13% achieved histologic remission	Distribution: 4.8 ± 1.3 L[k] Bioavailability: 61%–64% Half-Life elimination: unknown	Local injection site reactions, conjunctivitis, cutaneous herpesvirus infection, facial erythema, psoriasis, alopecia, eosinophilia, erythema multiform, serum sickness- like reaction, immune thrombocytopenia, erythema nodosum

TABLE 2 (Continued)

Biologic	Mechanism of action	Indications	Age	Route	Dosing schedule	Efficacy	Pharmacokinetics	Potential adverse effects
Tezepelumab	Blocks thymic stromal lymphopoietin binding to its receptor and subsequently decreases the production of eosinophils, IgE, IL-5, IL-13, and FENO	Severe asthma	≥12 years	s.q.	210 mg q4 weeks	93% decrease in exacerbations[l] 230 mL increase in FEV1	Distribution: 3.9 L[m] (central), 2.2 L (peripheral) Bioavailability: 77% Half-life elimination: 26 days	Hypersensitivity reactions
Tralokinumab	Blocks IL-13 binding to the IL-13 receptor	AD, moderate to severe	≥18 years	s.q.	Loading dose: 400 mg maintenance dose: 300 mg q2-q4 weeks based on weight or skin condition	AD[n]: 12.7% improvement in IGA 21.8% increase in EASI 75	Distribution: 4.2 L[o] Bioavailability: 76% Half-life elimination: 3 weeks	Increased URIs, conjunctivitis, keratoconjunctivitis

Note: Although all are monoclonal antibodies, the medication options vary in their treatment schedule, efficacy, and adverse effects.

Abbreviations: AD, atopic dermatitis; EASI, eczema area and severity index; EOE, eosinophilic esophagitis; EOS/HPF, eosinophils per high power field; FEV1, fraction of exhaled volume in 1 s; IGA, investigator global assessment; IgE, immunoglobulin E; ISS, itch severity score; OCS, oral corticosteroids; OR, odds ratio; PRO, patient-reported outcome; q, every; s.q., subcutaneous; UAS7, urticaria activity score over 7 days; URI, upper respiratory tract infection.

[a]30-32.

[b]58,59.

[c]Genentech. Xolair (omalizumab) for subcutaneous use prescribing information. South San Francisco, CA; September 2014.

[d]7,39,42,43.

[e]GlaxoSmithKline. Nucala (mepolizumab) for injection, for subcutaneous use and injection, for subcutaneous use prescribing information. Research Triangle Park, NC; September 2020.

[f]44.

[g]Teva. Cinqair (reslizumab) injection, for intravenous use prescribing information. Frazer, PA; June 2016.

[h]16,49,50.

[i]18,20,79,80.

[j]94.

[k]Sanofi-Aventis. Dupixent (dupilumab) injection for subcutaneous use prescribing information. Bridgewater, NJ. March 2017.

[l]21.

[m]Astra Zeneca and Amgen Inc. Tezspire (tezepelumab) prescribing information. Thousand Oaks, CA; December 2021.

[n]22,81.

[o]Adbry (tralokinumab-ldrm) [prescribing information] Madison, NJ: LEO Pharma Inc; January 2022.

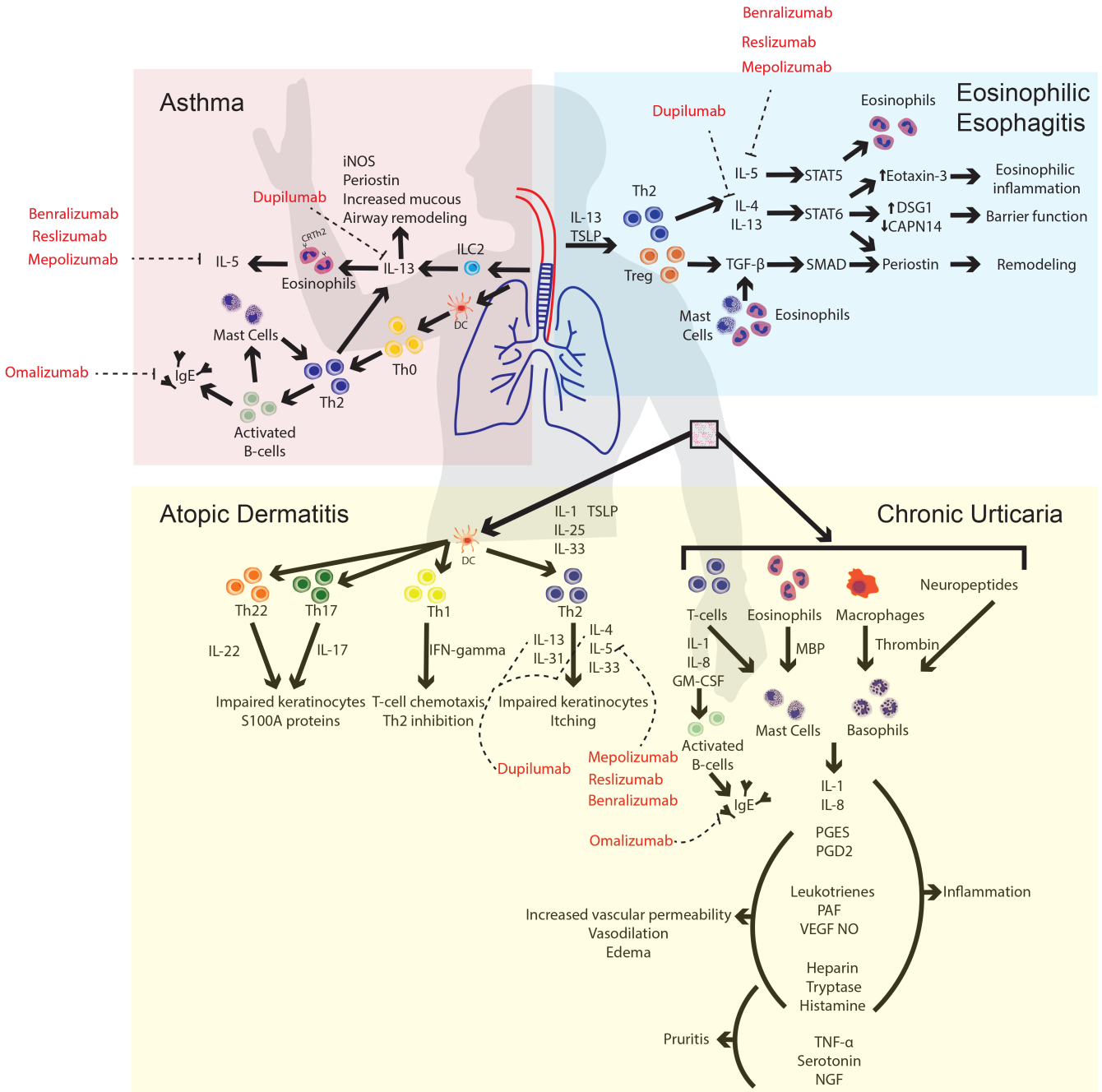

FIGURE 1 Cellular pathophysiology and drug targets for each discussed disease process.

Safety

Anaphylaxis is a serious potential adverse effect of omalizumab administration, and the FDA has applied a black box warning for this potential adverse effect. However, the incidence of anaphylaxis appears to be relatively low (reported as 1–2 in 1000 participants on therapy).[2] Other potential associated adverse effects revealed in long-term post-exposure safety studies include a small increase in cardiovascular and cerebrovascular events, including transient ischemic attack (0.7 in omalizumab treated participants vs, 0.1 in non–omalizumab-treated group per 1000 person years [PYs]) and myocardial infarction (2.1 in omalizumab exposed vs. 0.8 in non-omalizumab exposed per 1000 PYs). Additionally, increased incidence of pulmonary hypertension (0.5 vs. 0.0 per 1000 PYs) and unstable angina (2.2 vs. 1.4 per 1000 PYs) has been described in omalizumab exposed versus non-omalizumab exposed, respectively. However, these results were confounded by increased baseline risk of cardiovascular events in the study population prior to initiation of omalizumab.[3] Phase I/II

studies demonstrated an imbalance of patients with malignancy in omalizumab-treated patients compared to placebo. However, an additional registry study of over 5000 patients found no increased risk of malignancy among those being treated with omalizumab.[4]

Mepolizumab

Mepolizumab is a humanized mAb that binds to IL-5, preventing it from binding to its receptor (immunoglobulin G1 kappa 8). IL-5 regulates the growth, differentiation, recruitment, activation, and life cycle of eosinophils. IL-5 receptor blockade leads to reduced eosinophil growth, production, and survival[5] (see Figure 1).

Safety

A multicenter, long-term, open label safety study conducted in participants with asthma identified respiratory tract infection ($n = 5231$ [67%]), headache ($n = 599$ [29%]), worsening asthma ($n = 594$ [27%]), and bronchitis ($n = 573$ [21%]) as the most reported adverse events with mepolizumab treatment. In the study, 24 (7%) participants experienced an "on-treatment opportunistic infection," of whom 8 (2%) experienced herpes zoster infection (17 events per 1000 PYs). No specific populations were noted to be more at risk for this potential adverse event.[6] In a randomized, double-blind, placebo-controlled trial of mepolizumab administered s.q. every 4 weeks for 20 weeks among 135 participants with severe eosinophilic asthma, the two most reported adverse events were headache and nasopharyngitis.[7] Hypersensitivity reactions are listed as a precaution in the drug label. One study showed that 2% of participants on mepolizumab experienced allergic/hypersensitivity reactions; however, none were classified as anaphylaxis (Table 2).

Reslizumab

Reslizumab is an IgG4 κ humanized mAb composed of the complementary-determining regions of a murine antibody to human IL-5 that has been grafted onto human frameworks. The IL-5 receptor is a dimeric complex consisting of both α and βc subunits on the eosinophil cell surface. Activation of the receptor complex results in the activation of several signaling pathways, including JAK/STAT, MAPK, PI3K, and NF-κB, leading to transcription of genes involved

TABLE 2 Demographics and treatment options for each disease process.

Disease state	Population demographics[a]	mAbs	Other medical therapy	Surgical therapy
Asthma	Any age F > M in adults 8–10% of population	Omalizumab Mepolizumab Benralizumab Reslizumab Dupilumab Tezepelumab	Leukotriene receptor antagonists Inhaled glucocorticoids Inhaled glucorticoids combined with long acting B2 agonists Long-acting muscarinic agents Azithromycin	Bronchial thermoplasty
Chronic Urticaria	3rd-5th decade of life F > M 5% of population	Omalizumab	Antihistamines Including H1 and H2 blockers Leukotriene receptor antagonists Systemic immunosuppression	
Atopic Dermatitis	Onset usually in childhood 16% (children); 7.3% adults[b]	Dupilumab Tralokinumab	Topical corticosteroids Topical PDE4 inhibitors Topical calcineurin inhibitors Wet wrap therapy Bleach baths Topical JAK inhibitors House dust mite sublingual immunotherapy Subcutaneous immunotherapy	
Eosinophilic esophagitis	More recognized in children M > F 0.4% of population	Dupilumab	Food elimination diets Elemental diet Swallowed topical steroids	Esophageal dilations

Abbreviation: mAbs, monoclonal antibodies.

[a]Based on United States population data.

[b]Eczema prevalence in the United States: data from the 2003 National Survey of Children's Health; Shaw TE, Currie GP, Koudelka, Simpson; J Invest. Dermatology 2011.

in eosinophil differentiation, degranulation, survival, proliferation, chemotaxis, and adhesion[8] (see Figure 1). Reslizumab neutralizes circulating IL-5 by preventing binding to the alpha chain of the IL-5 receptor complex.

Safety

The FDA applied a black box warning on reslizumab for anaphylaxis risk; this adverse event occurred in 0.3% of participants in reslizumab clinical trials.[9] In the previously described study by Castro et al., the most common adverse event associated with reslizumab exposure was nasopharyngitis, which occurred in 11 participants (21%) in the reslizumab group versus five participants (9%) in the placebo group.[10]

Benralizumab

Benralizumab is a humanized IgG1κ, afucosylated, anti-IL5Rα mAb (see Figure 1). Without a fucose sugar residue in the CH2 region of the Fc domain, benralizumab binds with high affinity to the RIIIa region of the Fcg receptor found on NK cells, macrophages, and neutrophils, which induces antibody-dependent cell-mediated cytotoxicity of eosinophils and basophils. Benralizumab also binds with low affinity to the alpha-chain of the IL-5 receptor complex and blocks eosinophil signaling and proliferation.[11,12]

Safety

A reported potential adverse effect of benralizumab is hypersensitivity reactions, at a rate of 3% among participants exposed to the medication.[9] A randomized, placebo-controlled, double-blind, dose-ranging phase IIb study with adults ($n=606$) aged 18–75 years with uncontrolled asthma described that nasopharyngitis was reported in 44 (11%) of those receiving benralizumab versus 13 (6%) in the placebo group. Previous studies reported hypersensitivity at 3% for participants on benralizumab therapy.[13,14] A 2019 meta-analysis reported a higher risk of headache (risk ratio [RR]1.42, 95% confidence interval [CI] 1.07–1.87) and pyrexia (RR 2.26, 95% CI 1.32–3.87) among participants treated with benralizumab versus those on placebo.[15]

Dupilumab

Dupilumab is a fully human anti-IL-4 receptor alpha (IL-4Rα) immunoglobulin G4 subclass mAb that blocks both IL-4 and IL-13 signaling[16] (see Figure 1). Two known types of IL-4 receptors exist: the type I IL-receptor, comprised of IL-4Rα complexed with the γc chain, and the type II receptor, comprised of the common IL-4Rα and the α1chain of the IL-13 receptor (IL-13Rα1). IL-4 can bind to and activate the type I receptor and both IL-4 and IL-13 can bind to and activate the type II receptors. Type I and type II receptors are expressed on numerous inflammatory cells, such as B lymphocytes, eosinophils, dendritic cells, monocytes/macrophages, and basophils. Dupilumab inhibits signaling of IL-4 and IL-13 by targeting the common IL-4Rα subunit in both type I and type II receptors.

Safety

Reported adverse effects among adults exposed to dupilumab have included local injection site reactions (up to 18%), infectious and non-infectious conjunctivitis, cutaneous herpesvirus infections, and facial erythema.[17] Adverse effects observed in children on dupilumab include worsening of AD, conjunctivitis, skin infection, and upper respiratory tract infections.[18] Blood hypereosinophilia has also been reported as a potential adverse effect.[19] The dupilumab drug label recommends avoiding live vaccines during treatment; however, there are limited data to support this abstention. This recommendation is moreover based on pivotal trial design whereby participant exclusion criteria included receipt of live vaccines 3 weeks prior to study enrollment.[20]

Tezepelumab

Tezepelumab is a humanized monoclonal antibody IgG2λ targeted against thymic stromal lymphopoietin (TSLP). In the Th2 pathway, once epithelial injury occurs, there is a release of TSLP, IL-25, and IL-33, which help further drive the Th2 response. TSLP drives dendritic cells to promote the differentiation of naïve T cells into Th2 cells. In addition, TSLP can drive Th2 cytokine secretion from mast cells directly. Tezepelumab blocks TSLP binding to its receptor and subsequently decreases the production of eosinophils, IgE, IL-5, IL-13, and FENO.[21]

Safety

Hypersensitivity reactions are described in the drug label as possible adverse effect. The label also recommends avoiding live vaccines while on this drug. Last, the label recommends treating pre-existing parasitic infections; if a parasitic infection occurs while on tezepelumab, the

package insert recommends discontinuing the drug until the parasitic infection is treated completely.

Tralokinumab

Tralokinumab is a humanized IgG4 monoclonal antibody against IL-13 that blocks its binding to the IL-13 receptor. This prevents further release of Th2 cytokines and involvement of IgE.

Safety

The majority of adverse events associated with tralokinumab are increased upper respiratory tract infection, conjunctivitis, and keratoconjunctivitis. In a major phase III clinical trial, adverse events were reported at 71.4% compared to 66.4% in the placebo group and the majority were mild or moderate in severity.[22] Conjunctivitis occurred in 13.1% of patients on tralokinumab which was the major adverse event that led to discontinuation of the therapy.

DISEASE-SPECIFIC USE AND EFFICACY

Asthma

Asthma is a heterogenous disease characterized by chronic inflammation and recurrent, reversible bronchial obstruction.[23] Asthma prevalence varies based on age. Prevalence of asthma is estimated to be 5.8% in children less than 18 years and 8.4% in adults greater than 18 years. Prevalence in adulthood is skewed toward female patients and disproportionately affects those below the poverty threshold. Symptoms of asthma include shortness of breath, cough, chest tightness, and wheezing. Symptoms of airway obstruction are caused by reversible airway inflammation and variable airflow limitation. The underlying pathophysiology of asthma is characterized by inhaled allergens, microorganisms, and pollutants interacting with the airway epithelium, which triggers activation of mediators, such as mast cells, Th2 cells, TSLP, IL-25, and IL-33 further activating IL-4, IL-5, and IL-13. As previously described, IL-5 is important for recruitment, maturity, and survival of eosinophils. IL-5 also induces eosinophil chemotaxis into the intravascular space and migration to the lung through selectins, cadherins (adhering to lung endothelium), and integrins (eosinophils binding to intercellular adhesion molecule 1 [I-CAM1]). As eosinophils enter the matrix of the airway through influence of chemokines and cytokines, their survival is prolonged by IL-4 and granulocyte-macrophage colony stimulating factor (GM-CSF). Upon activation, eosinophils release leukotrienes and granule proteins, resulting in airway tissue injury. Eosinophils also generate GM-CSF to prolong their survival, contributing to persistent airway inflammation.[24]

Differing asthma phenotypes have been described, which include allergic asthma, non-allergic asthma, adult-onset asthma, asthma with persistent airflow limitation, and asthma with obesity.[25,26] Asthma phenotype is important in not only understanding underlying pathophysiology and the drivers of asthma but also may allow more precise therapeutic treatment. The advent of monoclonal antibody therapy has provided an opportunity to directly target underlying mediators of disease more specifically in asthma and therefore lead to improved outcomes for the significant proportion of patients with asthma who do not respond to inhaled corticosteroids.

Omalizumab

Omalizumab has been shown to reduce asthma exacerbations, improve symptoms, minimize the use of inhaled corticosteroids, reduce rescue medication use, and improve quality of life.[27] Measurable outcomes that showed the most benefit in relation to omalizumab therapy include reduction of exacerbation rates as well as reduction in oral and inhaled corticosteroid doses.[28,29]

A pivotal trial evaluated the effect of omalizumab on uncontrolled asthma despite participants being on combination therapy with inhaled corticosteroids and long-acting beta agonists. Patients age 12–75 years demonstrated a 25% relative reduction in exacerbation rate and an improvement in asthma quality of life scores (AQLQS) from baseline.[30] A subsequent trial evaluated participants between 6 and 11 years of age and demonstrated a risk reduction of exacerbation at 50%.[31] Omalizumab has demonstrated decreased risk of respiratory illness in patients with asthma as well.[32] In another trial, omalizumab was shown to reduce severe exacerbation rate by 50%, emergency visit rate by 44%, and improved FEV1% all compared to placebo.[33]

However, a large Cochrane database analysis of studies involving omalizumab treatment of asthma demonstrated that omalizumab treatment led to minimal improvement in FEV1, but a reduction in hospitalizations for those treated with omalizumab versus placebo (OR 0.16, 95% CI 0.06–0.42: four studies, 1824 participants). Additionally, participants on omalizumab were more likely to withdraw from the study compared to placebo, possibly due to adverse effects.

Mepolizumab

Mepolizumab has been shown to improve health-related quality of life, reduce asthma exacerbations, improve lung function, and reduce corticosteroid dependence.[34] A study was conducted in adult participants with severe eosinophilic asthma receiving maintenance treatment with systemic glucocorticoids. Investigators observed a 50% reduction in oral glucocorticoid dose in participants receiving mepolizumab treatment in comparison to those receiving placebo.[7] A large systematic review of randomized placebo-controlled trials of biologics used to treat asthma demonstrated that mepolizumab reduces incidence rate ratio of asthma exacerbations compared to placebo.[35] Analyses of two major phase III trials with mepolizumab compared to placebo showed 47% reduction rate compared to placebo.[36] Finally, a recent meta-analysis demonstrated a mean increase in FEV1 in asthma participants treated with mepolizumab from baseline to treatment after 12 weeks.[37]

Reslizumab

In trials, reslizumab reduced exacerbation rates by 50–59% with 4–7% improvement in FEV1 versus placebo in participants with an eosinophilic asthma phenotype. In two phase III trials in adolescents and adults with peripheral eosinophilia and asthma, reslizumab reduced annualized asthma exacerbation rates by 50% and 59% relative to placebo. Reslizumab treatment also demonstrated improved prebronchodilator FEV_1 from baseline in comparison with placebo by +126 mL and +90 mL. In addition, reslizumab treatment demonstrated improved quality of life measurements using the Asthma quality of Life Questionnaire tool.[38]

Benralizumab

Benralizumab reduces annual exacerbation rates in patients with eosinophilic asthma in trials up to 51%.[10,14] More specifically, benralizumab treatment decreased rates of asthma exacerbations more in patient populations with high eosinophil asthma versus low eosinophil asthma (35% vs. 17% reduction rate, respectively).[13] Patients with high-eosinophil levels also showed improvements in pre-bronchodilator FEV1 with either every 4 or 8 week dosing.[39] Additionally, benralizumab allows patients to reduce their oral steroid reliance.[40,41]

Dupilumab

In participants with severe eosinophilic asthma, dupilumab therapy was associated with fewer asthma exacerbations, improved lung function, and reduced levels of Th2-associated inflammatory markers.[19] Dupilumab has been shown to reduce exacerbation by 46–70% with 140 mL improvement in FEV1 versus placebo.[16] Dupilumab used subcutaneously every 2 weeks decreased eosinophilic asthma exacerbation rates by up to 67% compared to placebo.[42] Additionally, prebronchodilator FEV_1 improved by up to 140 mL compared with placebo. Oral steroid dose decreased by 70% (compared to 42% with placebo) and 48% of patients receiving dupilumab were able to discontinue oral steroids completely. Patients treated with the dupilumab group had a reduction in severe exacerbation rates compared to placebo.[43]

The majority of these studies are done in adolescents and adults ages 12 and older. An exciting development is the approval of dupilumab for children with asthma between the ages of 6 and 11. A phase III randomized placebo-controlled trial used weight-based dosing (100 mg for participants ″30 kg and 200 mg for those >30 kg) and demonstrated a significant reduction in the annualized rate of asthma exacerbations in the dupilumab arm compared to the placebo group with a relative risk reduction in the dupilumab group of 59.3%.[44]

Tezepelumab

Most recently, tezepelumab showed a reduction in annualized rates of asthma exacerbation compared to placebo (0.93 vs. 2.10). Additionally, baseline FEV1 in the tezepelumab arm was greater than placebo (0.23 L vs. 0.09 L respectively).[21]

Future therapy

Many potential targets are being evaluated for the future treatment of asthma, including anti- TSLP and prostaglandin D2 receptor antagonism, both known to inhibit the Th2 pathway earlier on compared to current more downstream targets (IgE, IL-4Ra, IL-5, and IL-5R). Phase II studies of tezepelumab, an anti-TSLP agent, noted improvements in the annualized exacerbation rate in participants treated with the biologic.[45] Fevipiprant, an investigational PD2 receptor antagonist, showed improvement in AQLQS in a limited study with 61 participants.[46] Additionally, a new category of therapeutic molecules, anti-CεmX-monoclonal antibodies (anti-CεmX-mab), is currently being evaluated. This category of monoclonal antibodies operates with an alternative mechanism of the IgE-mediated allergic inflammatory pathway as the molecule acts on the CemX domain of membrane-bound IgE and has a molecular target located further upstream than the direct blocking of circulating IgE. Anti-CεmX-mab binding on IgE-switched B lymphoblasts causes cellular lysis and prevents allergen-mediated generation of IgE-producing

plasma cells. As anti-CεmX-mab do not bind to free IgE, therapeutic effect may not depend on serum IgE levels in contrast to current thoughts regarding other mAbs involved with IgE targeting.[1]

Chronic urticaria

CU is characterized as the sporadic and spontaneous presence of urticarial lesions for 6 weeks or greater without a discoverable cause.[47] CU affects ~5% of the US population and can significantly impair quality of life. CU can affect both male and female patients but is more commonly reported among female patients; it most frequently presents in the third to fifth decade of life; however, it may also occur during childhood to early adulthood.[48] Approximately 20% of patients with CU have the chronic inducible or spontaneous urticaria type, which indicates that there is a reproducible trigger for urticaria such as a physical (e.g., pressure) or environmental stimuli (e.g., cold temperature).

The pathogenesis of CU is poorly understood. Development of urticaria results from mast cell degranulation and release of cell mediators, such as histamine, proteases, prostaglandins, leukotrienes, and cytokines.[49] This release and activation of mast cell mediators results in vasodilatation and increased vascular permeability of dermal superficial vasculature, which result in the characteristic "wheal" and "flare" type urticarial lesions.[50] Possible theories of pathogenesis include autoimmunity, cellular defects in mast cells and basophils, and presence of factors in the serum or plasma that cause histamine release. Currently, assays are available to measure IgG antibodies specific to the IgE receptor alpha subunit (anti-Fc-epsilon-R1-alpha) or the Fc region of IgE. The presence of these antibodies is observed in 30–40% patients with CU; however, their relation to CU pathogenesis remains poorly understood. Many biomarkers have been evaluated for prediction of response to therapy in patients with CU, including CRP, IL-31, D-dimer, C5a, and autologous serum skin test. Basophil count, IL-6, and IL-17 levels have also been evaluated as biomarkers for disease course and activity, but these currently lack data for clinical application. Studies do suggest that high serum IgE levels may predict response to omalizumab for treatment of CU and early response to omalizumab has been linked to the presence of IgE autoantibodies.[51]

Omalizumab

Omalizumab treatment is recommended in individuals with refractory CU despite anti-histamine therapy.[52] Disease control can be assessed by standardized scoring systems, including the Urticaria Activity Score over 7 days (UAS7) with a scale ranging from 0 to 42, with higher scores indicating greater activity, or itch severity score (ISS), which ranges from 0 to 21, with higher numbers indicating greater disease activity.[53]

Clinical trials have demonstrated efficacy of omalizumab for the treatment of CU in adolescents and adults. Two landmark[47,54] randomized, double-blinded, placebo-controlled trials demonstrated efficacy and safety of omalizumab for refractory CU in participants greater than or equal to 12 years. Both trials evaluated participants receiving s.q. omalizumab versus a placebo and observed statistically significant improvements in the UAS7,[55] ISS, weekly number of hives, and the Dermatology Quality of Life Index. Meta-analysis of seven randomized, placebo-controlled trials evaluated efficacy of omalizumab in 1312 participants with CU. Significant improvements are seen in itch and wheal scores with omalizumab 300 mg every 4 weeks. Although omalizumab demonstrates efficacy in reducing symptoms, these studies also demonstrate rapid symptom return after abrupt discontinuation of therapy. Therefore, current recommendations are to treat for 1 year at minimum before considering discontinuation in patients who have had complete resolution of symptoms.[56,57]

Future therapy

Current biologics under investigation for treatment of CU include dupilumab and ligelizumab. Dupilumab has shown efficacy at higher range dosing of 600 mg monthly in a limited number of participants.[58] There are ongoing phase IIa trials to evaluate the safety and efficacy of dupilumab for chronic idiopathic and spontaneous urticaria.[59] Ligelizumab is a high affinity monoclonal antibody targeting IgE. Phase II clinical trials have demonstrated superior response to ligelizumab compared to omalizumab.[60] Participants were randomized to receiving ligelizumab (at one of three doses), omalizumab 300 mg, or placebo. Participants in the ligelizumab arms had the most improvement in urticaria scores compared to omalizumab or placebo.

Additional targets under development for treatment of CU include Siglec-8, Chemoattractant receptor expressed on Th2 cells (CRTh2) antagonist, Bruton tyrosine kinase inhibitors, and Spleen tyrosine kinase (Syk) inhibitors.[59] Consideration of targets for future therapies include Mas-Related G Protein–Coupled Receptor X2, Histamine 4 receptor, C5a, CD88, inhibitory mast cell receptors, Il-33, IL-25, TSLP, and stem cell factor.[59]

Atopic dermatitis

AD is a chronic remitting–relapsing inflammatory skin condition characterized by pruritic, eczematous skin lesions with dry skin and erythema.[61] AD is the most common chronic cutaneous disease of children affecting 5–20% of children worldwide and is associated with other atopic and allergic diseases.[62–64] AD-related comorbidities include atopic keratoconjunctivitis, infections, obesity/metabolic syndrome, cardiovascular disease, and mental health disorders, such as anxiety and depression. Overall quality of life is additionally impacted among patients with AD, as patients report higher rate of sleep deprivation.[65]

The pathophysiology of AD is characterized by skin barrier defect, Th2 pathway imbalance, and altered skin microbiota. Gene mutations including loss of function *Filaggrin* (*FLG*) mutation have been implicated as a predisposing factor for AD. *FLG* is a skin barrier protein that helps maintain skin hydration and prevent invasion by microorganisms primarily through its byproduct called Natural Moisturizer Factor.[66] Overproduction of helper Th2 cytokines, such as IL-4, IL-5, and IL-13, is involved in pathogenesis of AD. More recently, epithelial derived cytokines, such as IL-25, TSLP, and IL-33 were recognized as contributors to AD pathophysiology.[67] These cytokines activate innate lymphoid cells type II (ILC-2); additionally, IL-33 downregulates β-defensins, which maintain skin integrity. Other contributors to AD pathophysiology include decreased tight junction related proteins; reduced toll-like receptor (TLR) 2 and TLR9 leading to further skin barrier defects.[68] As such, skin cultures of patients with AD often demonstrate *Staphylococcus aureus* (*S. aureus*) colonization. *S. aureus* associated superantigens further lead to IL-31 secretion contributing to pruritus and perpetuating inflammation.

The first-line therapeutic treatment for AD is topical steroids. An appropriate potency topical steroid should be chosen, as weak steroids may lead to suboptimal control of or even worsening of AD. Prolonged use of a high potency topical steroid can lead to epidermal atrophy.[69] Topical calcineurin inhibitors are an alternative to topical steroids used primarily in older patients due to adverse effect of skin burning sensation.[70] Crisaborole, a topical phosphodiesterase 4 inhibitor, is a treatment option for patients 3 months of age or greater with mild to moderate eczema.[71] Control of AD can be measured by the Eczema Area and Severity Index (EASI) score (scale of 0 to 72 with higher values indicating higher disease activity) and the Investigator Global Assessment (IGA; scale of 0–5 with higher values indicating higher disease activity).[72]

Dupilumab

Dupilumab was approved for the treatment of AD in adults in 2017. Two major phase III clinical trials evaluated outcomes for participants with AD who received dupilumab monotherapy compared to placebo.[20] In each of these studies, 36–38% of participants receiving dupilumab either weekly or every other week improved their IGA scores significantly compared to placebo (8–10%). Additionally, 75% of participants on dupilumab had a 75% improvement in EASI scores. Studies in children aged 6–11[73] and adolescents[18] have also noted improvements in IGA and EASI scores. A phase II study conducted over 4 weeks in children 6 months to 5 years of age showed an improvement in EASI and pruritus scores.[74]

Tralokinumab

Tralokinumab was approved for the treatment of moderate to severe AD in 2021. A study summarizing the findings of two major phase III clinical trials (ECZTRA I and ECZTRA II), described the efficacy of tralokinumab for AD after 16 weeks of therapy.[75] ECZTRA I reported IGA improvement in 15.8% of patients receiving tralokinumab compared to 7.1% receiving placebo and 25% improvement in EASI 75 in tralokinumab compared to 12.7% in placebo. ECZTRA II demonstrated similar findings with a 22.2% improvement in IGA compared to 10.9% in placebo and 33.2% improvement in EASI 75 in tralokinumab compared to 11.4% in placebo. An additional phase III study[22] demonstrated consistent findings with IGA score improvement achieved in 38.9% on those receiving tralokinumab compared to 26.2% on placebo and EASI 75 improvement in 56% on tralokinumab compared to 35.7% placebo.

Future therapy

Three multicenter randomized studies evaluated the use of upadacitinib, a Janus tyrosine kinase inhibitor, in severe AD. At 16 weeks of treatment, participants receiving upadacitinib had a 75% improvement in EASI score compared to placebo group.[76] Another JAK inhibitor, abrocitinib, was compared to dupilumab in the treatment of refractory AD in a phase III trial with 800 adults and demonstrated noninferiority of abrocitinib in comparison to dupilumab.[77]

Additional biologic treatments currently being investigated in the treatment of AD include therapeutics targeting IL-13,[78] IL-31,[79] and IL-22.[80] These agents have completed phase II trials with favorable results; however, large studies with longer duration are needed.

Eosinophilic esophagitis

Eosinophilic esophagitis (EOE) is a chronic Th2-predominant inflammatory disease characterized by eosinophilic infiltration of the esophagus. Potential triggers for EOE include food and/or environmental allergen exposures, particularly in difficult to treat refractory disease.[81] The disease is rare affecting an estimated 0.4% of the population in Western countries including children and adults. Male patients are affected more often than female patients. The pathophysiology is described as an allergen driven Th2 T cell response that triggers infiltration of eosinophils into the esophagus leading to inflammation, remodeling, and fibrosis. Antigen recognition by Th2 lymphocytes and dendritic cells leads to recruitment of basophils, mast cells, and eosinophils and production of proinflammatory cytokines interleukin-4, 5, 13, TSLP, eotaxin 3, prostaglandin D2 receptor IgE, IgG4, eosinophil derived granular proteins, and bone morphogenic protein.[82] The diagnosis of EOE is made when greater than or equal to 15 eosinophils per high-powered field are found on esophageal mucosal biopsy samples taken during esophagogastroduodenoscopy.[83] Active inflammation leads to dysphagia, odynophagia, and, in younger patients, vomiting, abdominal pain, and poor growth. Chronic inflammation results in fibrosis causing strictures and dysmotility. In vitro and in vivo studies have demonstrated the role of IL-4, 5, and 13 in promoting eosinophilic inflammation, loss of barrier function, and tissue remodeling in the esophagus.[84]

Based on known pathophysiology of EOE, investigators developed new biologic therapies specifically targeting interleukin pathway intermediates (e.g., IL-4, IL-5, and IL-13; Figure 1). Early studies explored targeting IL-5 based on the cytokine's ability to induce eosinophil trafficking to the esophagus in transgenic mice and its early promise in reducing peripheral eosinophilia in clinical trials.[85] Most recently, dupilumab became the first biologic approved by the FDA for treatment of eosinophilic esophagitis in children and adults 12 years and older.

Dupilumab

Dupilumab is the first FDA approved biologic for treatment of EOE in May 2022. An industry sponsored, phase II study of subcutaneous dupilumab in adults with active EOE evaluated patient-reported outcomes (PROs) and esophageal histologic response and endoscopic appearance. PRO scores in patients receiving the dupilumab improved (least squares mean change, −3.0) versus placebo (−1.3 $p = 0.0304$). For some, improvement in dysphagia started as early as week 1. For histologic response, 82.6% of patients receiving dupilumab achieved less than 15 EOS/high powered field (HPF) on histology (0% with placebo), and 13% achieved less than 1 EOS/HPF (0% with placebo). Esophageal distensibility plateau improved by 18.0% (2.9 mm) at week 12.[86] Phase III trials extended the age group into adolescents and published interim data demonstrated improvement in quality of life measures and symptoms at week 24 of treatment.[87]

Mepolizumab

Mepolizumab was first investigated for use in EOE in 2006 with an open label trial followed by a randomized control trial (RCT) in 2010.[88,89] Unfortunately, no patients in the RCT achieved the primary outcome of esophageal eosinophils less than 15 at the long-term follow-up point (34 weeks).

Reslizumab

Pediatric participants (5–18 years old) with moderate to severe EOE symptoms were eligible for a double-blind, placebo-controlled trial of reslizumab in 2012.[90] After 3 months, median and mean esophageal eosinophil counts were below 50 EOS/HPF in all treatment groups. Diet changes were allowed, but most participants kept their current diet (~85% or participants in the treatment groups and 75% in the placebo group). An open-label follow-up study 9 years later re-evaluated participants who continued reslizumab monthly for 3–9 years and noted that 92% of participants experienced reduced esophageal eosinophils to less than 5/HPF. No participants were on steroids, and few were on diet restrictions in this study.

Omalizumab

IgE notably has been reported to be elevated in those with EOE compared to controls,[91] and previous studies have demonstrated potential benefit of omalizumab in the treatment of eosinophilic gastrointestinal disease outside the esophagus.[92] However, the role of omalizumab in EOE pathogenesis is undefined, and although two studies have investigated s.q. omalizumab as treatment for EOE, neither found significant benefit in histological eosinophil infiltration or symptoms.[93]

Future therapy

Targets outside of the interleukins have also shown promise. CRTh2 receptor is found on lymphocytes, eosinophils, and basophils and mediates chemotaxis in response to mast cell

signals.[94] OC000459 is the only investigated non-steroidal oral therapy for EOE and is designed to block activation of CRTh2-expressing cells.[95] An RCT followed 26 participants for an 8-week course of OC000459, 100 mg taken twice per day. At follow-up endoscopy, the total eosinophils decreased significantly from 114.83 to 73.26 eosinophils/HPF. The physician's global assessment of disease also improved.

CONCLUSIONS

The landscape of biologics used to treat allergic conditions has expanded rapidly over the past several years and continues to expand. This review summarized the associated pathophysiology of common allergic conditions, including AD, asthma, EOE, and CU, and discussed current efficacy and safety data for biologic medications in the treatment of allergic disease. Targeting of underlying pathophysiology specific to allergic disease conditions presents an opportunity to provide more effective treatment, especially as we gain improved understanding of the nuances of the drivers of such conditions and specific disease phenotypes. In addition, by targeting more specific molecular targets, monoclonal antibody therapies may be generally associated with less systemic side effects than other anti-inflammatory treatments. The mAb therapies provide the opportunity to move closer to precision therapeutic treatment for complex allergic/inflammatory conditions.

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