

Biologic Therapy and Novel Molecular Targets of Severe Asthma



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

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List of Design Committee Members: Amber N. Pepper, MD, Harald Renz, MD, Thomas B. Casale, MD, and Holger Garn, PhD

Learning objectives:

1. To define asthma endotypes and understand how they can help guide therapy.
2. To understand the mechanisms of action, indications, and therapeutic effects of currently available and emerging biologics for the treatment of severe asthma.
3. To make informed therapeutic decisions regarding the use of biologic therapies in patients with asthma.

Recognition of Commercial Support: This CME has not received external commercial support.

Disclosure of Significant Relationships with Relevant Commercial Companies/Organizations: H. Renz has received consultancy fees from Sterna Biologicals GmbH & Co KG. T. B. Casale has received consultancy fees from AstraZeneca, Teva, Sanofi/Roche, Genentech, and Novartis; is Executive Vice President of the American Academy of Allergy, Asthma & Immunology; and has received research support from AstraZeneca, Sanofi/Roche, Genentech, and Novartis. H. Garn has received consultancy fees from and has stock/stock options in Sterna Biologicals and GmbH & Co KG. A. N. Pepper declares no relevant conflicts of interest.

Treatment options for severe or uncontrolled asthma are increasing, especially pertaining to novel biologic therapies. The 2 primary asthma endotypes, T2 high and T2 low, are defined by the level of type 2 T helper and innate lymphoid cell activity and mediators.

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Conflicts of interest: H. Renz has received consultancy fees from and has stock/stock options in Sterna Biologicals GmbH & Co KG. T. B. Casale has received consultancy fees from AstraZeneca, Teva, Sanofi/Roche, Genentech, and Novartis; is Executive Vice President of the American Academy of Allergy, Asthma & Immunology; and has received research support from AstraZeneca, Sanofi/Roche, Genentech, and Novartis. H. Garn has received consultancy fees from and has stock/stock options in Sterna Biologicals and GmbH & Co KG. A. N. Pepper declares no relevant conflicts of interest.

Received for publication March 24, 2017; revised manuscript received and accepted for publication April 27, 2017.

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2213-2198

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<http://dx.doi.org/10.1016/j.jaip.2017.04.038>

Most therapies for severe asthma target T2 high asthma, including the 3 biologics approved for use in the United States and Europe: omalizumab, mepolizumab, and reslizumab. Other biologics, with various molecular targets, are under investigation. Unfortunately, treatment options for T2 low asthma are limited. Although these therapies may improve asthma symptoms, exacerbation rates, and lung function parameters, they have not been shown to modify the disease process or provide lasting benefits after discontinuation. Biomarkers identified thus far to help guide individualized therapy in severe asthma are helpful, but imperfect discriminators for picking the best option for individual patients. This review will discuss the mechanisms of action, indications, and therapeutic effects of currently available and emerging biologics for the treatment of severe or uncontrolled asthma. © 2017 American Academy of Allergy, Asthma & Immunology (*J Allergy Clin Immunol Pract* 2017;5:909-16)

Key words: Asthma; Biologic; Monoclonal antibody; Precision medicine; Severe asthma; Eosinophilic asthma

Asthma is a heterogeneous disease that encompasses a wide range of clinical presentations and underlying disease processes.

Abbreviations used

CXCR2-CXC chemokine receptor 2
DP2-Prostaglandin D2 receptor 2
ICS-Inhaled corticosteroid
ILC2-Type 2 innate lymphoid cell
TSLP-Thymic stromal lymphopoeitin

This heterogeneity results in varying responses to therapies. Those with severe disease remain uncontrolled despite conventional therapies, such as inhaled corticosteroids (ICSs), inhaled bronchodilators, and oral leukotriene modifiers.¹⁻³ The repertoire of biologic agents for the treatment of severe asthma is expanding and a classification system, with relevant biomarkers, is needed to help guide tailored, stratified treatment decisions. Asthma can be organized into phenotypes, on the basis of observable and/or clinical characteristics. These include triggers (allergen or aspirin sensitivity), inflammatory cell milieu (eosinophilic vs neutrophilic or paucigranulocytic), and presence or absence of nasal polyposis, among other features.⁴ Endotypes, based on the pathophysiology of the disease, may provide more information for precision medicine and individualized treatments.^{1,4} The 2 primary asthma endotypes are characterized by high or low T_H2 cell and type 2 innate lymphoid cell (ILC2) activity, termed T2 high and T2 low, respectively.⁵ Most novel biologic treatments aim to treat T2 high asthma and the therapeutic options for T2 low asthma are limited (Table I; Figure 1).^{4,24} This review will discuss the mechanisms of action, indications, and therapeutic effects of currently available and emerging biologics for the treatment of severe or uncontrolled asthma.

T2 LOW ASTHMA

The pathophysiology of T2 low asthma is not well understood, but is characterized by the absence of T2 markers of activation and downstream signatures, such as eosinophilia. Instead, T2 low asthma is marked by neutrophilic or paucigranulocytic inflammation as a result of the activation of T_H1 and/or T_H17 cells and the release of their specific cytokines, such as IFN- γ and IL-17.^{1,4} In addition, T2 low inflammation may be driven by the release of other proinflammatory cytokines, such as TNF- α , IL-1 β , IL-6, IL-8, and the IL-12 family.^{1,4} Subjects with T2 low asthma usually have a later disease onset, lack a history of environmental allergies, and are less responsive to corticosteroids.

Unfortunately, there is paucity of treatment options for this population.^{4,25} There is an urgent need for novel therapeutic strategies for the treatment of T2 low asthma. In subjects with moderate-to-severe T2 low asthma, macrolide antibiotics have been shown to improve neutrophilia-associated markers and quality of life, but not lung function or asthma control.²⁶ Several clinical trials assessing potential biologic therapies for T2 low asthma, discussed below, have failed to show consistent clinically or statistically significant benefits. This may indicate that the absence of T2 high inflammation does not completely identify an asthma endotype or, alternatively, that the chosen targets are not key elements in the pathophysiology of T2 low asthma. However, many initial studies did not enrich for the appropriate patient population to study therapeutic effects. The pathophysiologic pathways of non-T2 inflammation need to be better understood to identify future successful therapeutic targets.

Targeting TNF- α

TNF- α is a central cytokine in various innate and/or non-T2 inflammatory pathways and there is evidence for an upregulation of the TNF- α axis in some subjects with refractory asthma.²⁷ Several monoclonal antibodies (mAbs) (adalimumab, golimumab, infliximab) and the TNF-receptor-immunoglobulin G1 fusion protein, etanercept, were investigated in clinical trials, but failed to show consistent or clinically meaningful efficacy.²⁷⁻³¹ Furthermore, unwanted side effects, such as increased infection and cancer rates, ceased the development of TNF- α -directed therapies for asthma.³¹

Targeting the T_H17 pathway

The T_H17 pathway is another potential target for the treatment of chronic inflammatory diseases, including asthma.³² Members of the IL-17 cytokine family, released predominantly by T_H17 cells, are key mediators of neutrophilic inflammation and may play a role in corticosteroid hyporesponsiveness in asthma.^{33,34} Thus, inhibition of the T_H17 pathway has been investigated for the treatment of T2 low or neutrophilic asthma.³⁵ Secukinumab, a mAb against IL-17A, did not significantly reduce neutrophils in a model of ozone-induced neutrophilia in healthy volunteers.³⁶ Studies in subjects with a noneosinophilic asthma phenotype are in progress with CJM112, a second-generation mAb against IL-17. Brodalumab, a mAb directed against the IL-17 receptor, blocks the signaling of IL-17A, IL-17F, and IL-17E (also called IL-25, a T2-associated cytokine). Brodalumab improved asthma control and symptoms in a subpopulation of subjects with greater than 20% post-bronchodilator FEV₁ improvement, but showed no efficacy in subjects with nonphenotyped severe asthma or in subpopulations identified by the presence of eosinophils or neutrophils.³⁷ Brodalumab development for asthma has been halted because of reports of increased suicide risk.

IL-23, a member of the IL-12 cytokine family, is essential for the differentiation and activation of T_H17 cells.^{32,38} A high-affinity humanized anti-IL-23A mAb, BI 655066 (risankizumab), is effective for the treatment of moderate-to-severe psoriasis and is under investigation as add-on therapy for the treatment of severe asthma in an ongoing clinical trial.³⁸⁻⁴⁰

Targeting GM-CSF

Another potential target investigated for the treatment of T2 low or neutrophilic asthma (as well as eosinophilic asthma) is GM-CSF. GM-CSF promotes neutrophil and eosinophil differentiation, recruitment, activation, and survival.⁴¹ An anti-GM-CSF mAb did not improve FEV₁ in the overall study population of patients with asthma inadequately controlled on standard inhaled and oral therapies. Statistically significant FEV₁ improvements were shown in the eosinophilic subpopulation, subjects with FEV₁ reversibility of 20% or more at baseline, and subjects with FEV₁ of less than or equal to 50% predicted at baseline. Asthma control and exacerbation rates did not improve.⁴²

Targeting CXC type chemokine receptor 2

IL-8 (also called chemokine ligand 8) binds to the CXC type chemokine receptor 2 (CXCR2) and stimulates neutrophil chemotaxis to sites of inflammation. Thus, inhibition of this receptor might represent a promising approach for the treatment of neutrophil-predominant asthma.⁴³ Despite demonstration of reduced sputum neutrophils in subjects with severe asthma in an initial study using a small molecule inhibitor of CXCR2 and

TABLE I. Approved and emerging biologic therapies for the treatment of severe asthma²

Approved in the United States and Europe					
Biologic	Mechanism	Requirements (per FDA)	Dosing	Efficacy	Additional relevant information
Omalizumab ⁶⁻⁹	Binds to IgE Decreases expression of FcεR1	Subjects ≥6 y old with moderate-to-severe persistent asthma inadequately controlled on ICSs Positive skin test result or <i>in vitro</i> reactivity to a perennial aeroallergen	75-375 mg SC Q 2 or 4 wk, based on serum total IgE and body weight	Reduces exacerbations (~40%; 60% if blood eosinophils ≥300 cells/μL) Improves quality of life	Improved responses with ↑FENO and blood eosinophils ≥300 cells/μL
Mepolizumab ¹⁰⁻¹²	Binds to IL-5	Subjects ≥12 y old with severe asthma with an eosinophilic phenotype as add-on maintenance treatment	100 mg SC Q 4 wk	Reduces exacerbations (~47%-53%; 79% if blood eosinophils ≥500 cells/μL) Improves FEV ₁ (~0.100 L; 0.132 L if blood eosinophils ≥500 cells/μL)	Phase 3 studies: blood eosinophil count ≥150 cells/μL at screening or ≥300 cells/μL in the past year Most efficacious if blood eosinophil count ≥500 cells/μL
Reslizumab ¹³⁻¹⁶	Binds to IL-5	Subjects ≥18 y old with severe asthma with an eosinophilic phenotype as add-on maintenance treatment	3 mg/kg IV Q 4 wk	Reduces exacerbations (~50%-60%) Improves FEV ₁ (~0.100-0.160 L; 0.270 L in subgroup analysis from 1 study) ¹⁴	Phase 3 studies: blood eosinophil count ≥400 cells/μL
In clinical development					
Biologic	Mechanism	Notable pivotal trial inclusion criteria	Likely dosing	Efficacy	Additional relevant information
Benralizumab ¹⁷⁻¹⁹	Binds to IL-5 receptor α present on eosinophils and basophils Induces ADCC	Subjects 12-75 y old with asthma inadequately controlled on ICS + LABA ± oral steroids with ≥2 exacerbations in the past year Blood eosinophil count ≥300 cells/μL	30 mg SC Q 8 wk (first 3 doses Q4 wk)	Reduces exacerbations (~28%-51%) Improves FEV ₁ (~0.100-0.160 L)	Phase 3 trials completed Effective, to a lesser extent, if blood eosinophil count <300 cells/μL
Dupilumab ²⁰	Binds to IL-4 receptor α Blocks signaling of IL-4 and IL-13	Subjects ≥18 y old with asthma inadequately controlled on medium-to high-dose ICS + LABA with ≥1 exacerbation in the past year	300 mg SC Q 2 wk	Reduces exacerbations (~60%-80%) Improves FEV ₁ (~0.150-0.160)	Phase 2b trial completed Effective across all groups, but most effective if blood eosinophil count ≥300 cells/μL
Tralokinumab ²¹	Binds to IL-13	Subjects 18-75 y old with severe asthma inadequately controlled by high-dose ICS + LABA with 2-6 exacerbations in the past year	Not yet determined SC	Improves FEV ₁ (~0.130 L)	Phase 2b trial completed Most effective in subjects with elevated DPP-4 or periostin
SB010 ²²	GATA-3 mRNA-specific DNase	Early and late- phase asthmatic response upon allergen challenge, presence of sputum eosinophils	Not yet determined	Improvement in early and late- phase FEV ₁ AUC	Phase 2a trial completed
AMG 157 ²³	Binds to TSLP	Positive skin prick test result, airway hyperresponsiveness upon allergen challenge	Not yet determined	Improvement in early and late- phase FEV ₁ AUC	Phase 2a trial completed

ADCC, Antibody-dependent cell-mediated cytotoxicity; AUC, area under the curve; DPP-4, dipeptidyl peptidase-4; FcεR1, high-affinity IgE receptor; FDA, US Food and Drug Administration; FENO, fractional exhaled nitric oxide; IV, intravenous; LABA, long-acting beta2 agonist; Q, every; SC, subcutaneous; TSLP, thymic stromal lymphopoietin.

This table includes only approved and emerging therapies under development with published human clinical trial data. Adapted from Casale.²

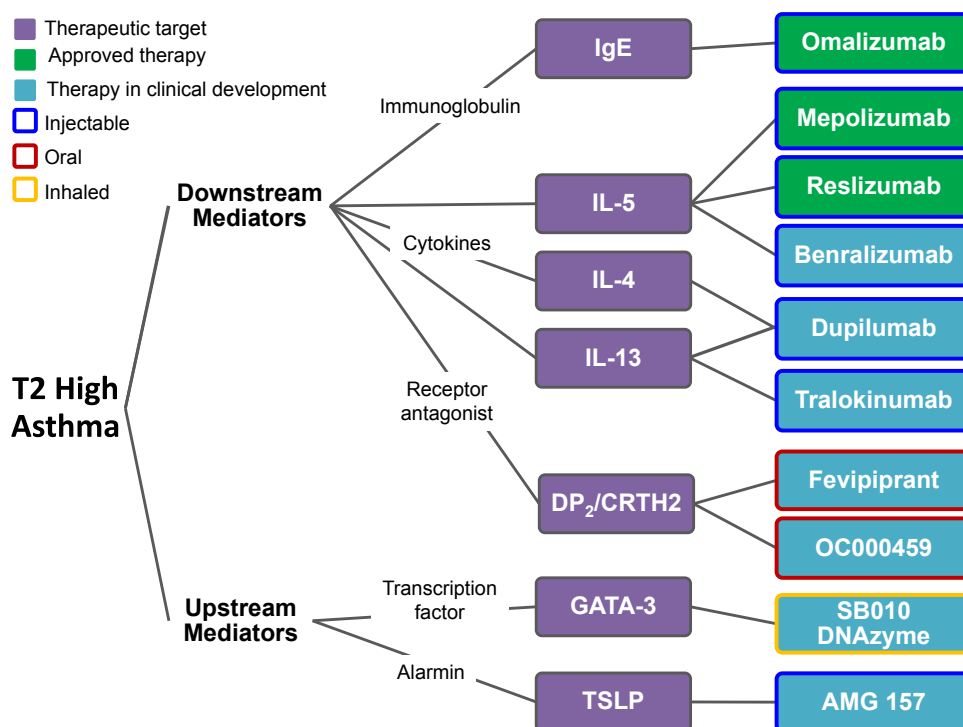


FIGURE 1. Biologic and novel therapies for the treatment of severe asthma. This figure includes only approved and emerging therapies with published human data. *CRTH2*, Chemoattractant receptor-homologous molecule expressed on T_H2 cells; *DP2*, prostaglandin D2 receptor 2; *IgE*, immunoglobulin E; *IL*, interleukin; *TSLP*, thymic stromal lymphopoietin.

CXCR1, a subsequent larger clinical trial examining a more specific CXCR2 inhibitor did not reduce the frequency of severe exacerbations in subjects with uncontrolled severe asthma.^{44,45} Thus, a combined blockade of CXCR2 and CXCR1 may be a more effective approach for neutrophilic asthma treatment.⁴⁶

T2 HIGH ASTHMA

T2 high asthma is characterized by eosinophilic inflammation and elevated type 2 cytokines, such as IL-4, IL-13, and IL-5.^{1,4,47} Both T_H2 cells and ILC2s produce these cytokines and are regulated by the transcription factor GATA-3.^{3,48} IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are epithelial-derived mediators that regulate the expression of type 2 cytokines.²⁵ Prostaglandin D₂ is produced in large quantities by activated mast cells and in smaller amounts by T_H2 cells and dendritic cells. Signaling through its receptor, prostaglandin D₂ receptor 2 (DP₂) or chemoattractant receptor-homologous molecule expressed on T_H2 cells, induces chemotaxis and activation of T_H2 lymphocytes, eosinophils, and basophils.⁴⁹ Several of these cytokines and their downstream mediators (eg, IgE) are targets of biologic therapies. Subjects with T2 high asthma are more likely to improve with corticosteroid treatment, but outcomes are variable.²⁵ In addition to blood and sputum eosinophilia, fractional exhaled nitric oxide, serum periostin, and dipeptidyl peptidase-4 are biomarkers of T2 high asthma and may help predict responses to certain biologic therapies.^{1,3} Several sub-endotypes of T2 high asthma exist that may also help predict therapeutic responses, including IgE-high, IL-5 high, and IL-13 high (Figure 1).¹

Targeting IgE

Approximately 70% of patients with asthma have an allergic phenotype, characterized by specific IgE to aeroallergens (skin prick or *in vitro* testing) and, in many cases, an elevated total serum IgE.⁶ The first biologic approved in the United States and Europe for the treatment of asthma, omalizumab, is a humanized mAb that binds to IgE. Omalizumab also leads to down-regulation of the high-affinity IgE receptor (FcεR1) on mast cells, basophils, and circulating dendritic cells.⁶ In the United States, omalizumab is approved for the treatment of moderate-to-severe asthma in subjects inadequately controlled on ICSs with documented sensitivities to 1 or more perennial aeroallergens.⁷ Requirements for use in Europe are similar, but eligible subjects must have severe persistent asthma.⁵⁰ Omalizumab is approved in children 6 years and older, the youngest age indicated for currently approved biologics.^{7,50}

Treatment with omalizumab significantly reduces asthma exacerbation rates, ICS use, and asthma symptoms. It may also improve asthma-related quality of life.^{6,51} However, improvements in lung function are less consistent.^{2,51} Omalizumab most effectively reduces asthma exacerbations in subjects with elevated T2 high biomarkers, including blood eosinophils and fractional exhaled nitric oxide.⁸ Specifically, a blood eosinophil count of 300 cells/μL or more predicts a more favorable response to omalizumab, with a 60% reduction in asthma exacerbations in one study.⁹ There is a small risk of anaphylaxis (0.1%) in subjects treated with omalizumab.⁷ The optimal duration of therapy, as with other mAbs for the treatment of asthma, is not well understood.⁶

Several other biologic therapies that target IgE have been investigated. These include a high-affinity anti-IgE mAb (ligelizumab), an anti-CD23 mAb (lumiliximab), and an anti-M1-prime mAb (quilizumab). These biologics are no longer being studied for the treatment of asthma because of a lack of clinical efficacy or superiority over omalizumab.²

Targeting IL-5

Patients with asthma and increased peripheral blood eosinophils experience more severe exacerbations and poorer overall asthma control.^{52,53} Targeted therapies for this phenotype of T2 high asthma are therefore needed. IL-5 is critical for eosinophil proliferation, activation, and recruitment, making it an appropriate therapeutic target in eosinophilic asthma.^{47,54}

As of March 2017, 2 biologic therapies targeting IL-5, mepolizumab and reslizumab, are approved and commercially available in the United States and Europe. Another, benralizumab, is in clinical development and likely to be approved in the near future. These agents can be used as add-on therapy in subjects with inadequately controlled asthma with an eosinophilic phenotype. Mepolizumab and reslizumab both target and bind to IL-5 directly, whereas benralizumab targets the IL-5 receptor alpha subunit.^{54,55} The mechanism of action of benralizumab allows it to mediate antibody-dependent cell-mediated cytotoxicity of eosinophils, basophils, and bone marrow eosinophil progenitors.^{56,57} Eosinophils may migrate into tissues through IL-5-independent mechanisms, making the direct mechanism of action of benralizumab theoretically advantageous over the more passive effects of reslizumab and mepolizumab.^{13,17,18,54}

Direct comparisons of the biologic therapies targeting IL-5 do not exist in the literature and an indirect meta-analysis found no clear superiority among the 3 therapies.⁵⁸ All 3 therapies can improve prebronchodilator FEV₁ and reduce asthma exacerbation rates.^{10,11,14,15} Reslizumab may elicit the greatest improvements in FEV₁.¹³⁻¹⁵ Benralizumab demonstrated a smaller reduction in exacerbations in 1 of the 2 phase 3 trials, SIRICCO and CALIMA, published in September 2016.^{17,18} All 3 biologics may also improve asthma control and quality-of-life scores, but the magnitude of improvement is small and the clinical impacts of these improvements are less clear. Comparisons between the 3 therapies are made more difficult by a lack of clearly defined biomarkers classifying the eosinophilic phenotype of asthma. The minimum peripheral blood eosinophil count used to define eosinophilia varies in the pivotal trials of each biologic (Table I). Trials of mepolizumab used blood eosinophil counts of 150 cells/μL or more at initiation or 300 cells/μL or more at any point in past year, trials of reslizumab used 400 cells/μL or more at initiation, and trials of benralizumab used 300 cells/μL or more at initiation.^{10,11,13,14,17,18} Benralizumab is efficacious in subjects with blood eosinophil levels lower than the limit used in the trials, but results were better in subjects with higher blood eosinophil levels, similar to what has been demonstrated for mepolizumab and reslizumab.^{10,13,14,17,18}

The dosing and frequencies of the 3 therapies targeting IL-5 also differ (Table I). Mepolizumab is administered subcutaneously in a fixed dose every 4 weeks.¹² Reslizumab is administered intravenously every 4 weeks and the dosing is weight-based, although a fixed-dose subcutaneous preparation is in development.¹⁶ Benralizumab is efficacious when administered in a fixed subcutaneous dose every 8 weeks, after the first 3 doses are given

every 4 weeks.^{17,18} The less frequent dosing of benralizumab may improve patient compliance and is a potential advantage over the other anti-IL-5 therapies. In addition, a single dose of intravenous benralizumab administered in the emergency department to patients presenting with an asthma exacerbation reduced subsequent exacerbation rates by 49% and exacerbations requiring hospitalization by 60% over 12 weeks in a small randomized controlled trial.⁵⁹ This suggests a novel role for the use of biologics, specifically benralizumab, in the emergency department to reduce asthma exacerbation relapses and health care costs.

The safety profiles for all 3 anti-IL-5 biologics are generally favorable. The package insert for mepolizumab suggests consideration of varicella zoster vaccination before treatment initiation due to an increased risk of shingles outbreaks.¹² Reslizumab is associated with rare (0.3%) cases of “anaphylaxis.”¹⁴⁻¹⁶ “Systemic reactions,” including anaphylaxis, occur with mepolizumab and “hypersensitivity” reactions with benralizumab.^{10,11,17,18} All biologics have the potential to cause anaphylaxis and patients should be aware of this risk. The optimal duration of these therapies is not well described. Upon stopping mepolizumab treatment, one study showed that subjects with asthma developed an increased frequency of severe asthma exacerbations, blood eosinophil counts, and worsening asthma symptoms.⁶⁰

Targeting IL-4 and/or IL-13

IL-4 and IL-13 are key T2 high cytokines and are thus attractive prospective targets for asthma biologic therapies. Both cytokines promote the class switching of B cells to produce IgE and induce the expression of vascular cell adhesion molecule 1 on vascular endothelium, promoting the recruitment of lymphocytes, monocytes, eosinophils, and basophils.^{47,61,62} IL-13 also stimulates airway goblet cell hyperplasia and IL-4 aids in the polarization of T cells into T_H2 cells.⁴⁷

Dupilumab, a fully human mAb directed against the IL-4 receptor alpha subunit, inhibits signaling of IL-4 and IL-13. It is efficacious in atopic dermatitis, nasal polyposis, and, as evidenced in a phase 2b trial, persistent asthma not adequately controlled by medium-to-high-dose ICS plus a long-acting beta₂ agonist.²⁰ In this trial, asthma exacerbation rates decreased by 71.2% to 80.7% and 59.9% to 67.6%, in subjects given subcutaneous dupilumab every 2 weeks with blood eosinophil counts of 300 or more or less than 300 cells/μL, respectively. Dupilumab, given every 2 weeks, also improved prebronchodilator FEV₁ as compared with placebo in all subjects, with the greatest effects in those with blood eosinophil counts of 300 cells/μL or more.²⁰ Based on these data, dupilumab appears to be effective when dosed every 2 weeks. It is most effective in subjects with blood eosinophil counts of 300 cells/μL or more, but may also be effective in those with lower eosinophil counts. Pitakinra, an IL-4 mutein that binds to the IL-4 receptor alpha subunit thereby targeting IL-4 and IL-13 signaling, is no longer in clinical development for the treatment of asthma.⁴

Biologics directed against IL-13 alone are also under clinical study and development. Serum periostin and dipeptidyl peptidase-4 are induced by IL-13 and predict response to these therapies.¹ Tralokinumab and lebrikizumab are 2 mAbs that bind to IL-13. Phase 3 trials of lebrikizumab for the treatment of uncontrolled asthma failed to show consistent, statistically significant reductions in exacerbation rates, even in subjects selected for elevated biomarkers (elevated periostin or blood

eosinophils).⁶³ Lebrikizumab is no longer being developed for the treatment of asthma. In a phase 2b trial, tralokinumab did not reduce asthma exacerbation rates in unselected subjects with uncontrolled asthma, but did improve prebronchodilator FEV₁ when given every 2 weeks. Improvements were larger in a subgroup analysis of subjects with elevated dipeptidyl peptidase-4 or periostin, but did not achieve statistically significant exacerbation rate reductions.²¹

Targeting GATA-3

The aforementioned treatment options target downstream products of T_H2 activation, but it may be advantageous to target upstream mediators that have the ability to block multiple T₂ pathways simultaneously. GATA-3 is the master transcription factor of T₂ immune responses. It is essential for T_H2 cell differentiation and activation as well as the production of all major T₂ cytokines (IL-4, IL-5, IL-9, and IL-13) by T_H2 cells and ILC2s. Moreover, GATA-3 is expressed in various effector cells of the allergic inflammatory response, including eosinophils, mast cells, basophils, and some epithelial cells.⁶⁴ The major challenge for the development of therapies targeting GATA-3 is the obligatory intracellular nature of this transcription factor. However, within the last 2 decades, antisense molecules that interfere with mRNA and inhibit the translation of proteins have been developed for clinical application in various diseases.⁶⁵ SB010 is an inhaled GATA-3-specific DNzyme, an enzymatically active single-stranded DNA oligonucleotide that specifically binds and cleaves GATA-3 mRNA. In early clinical trials, it appears to be safe and well tolerated.⁶⁶ SB010 significantly suppressed early and late-phase asthmatic responses and reduced T₂ biomarkers, such as sputum eosinophils and plasma IL-5 levels, after allergen challenge.²² Further clinical studies are needed to prove clinical efficacy in subjects with severe asthma.⁶⁷

Targeting DP₂ or chemoattractant receptor-homologous molecule expressed on T_H2 cells

DP₂ or chemoattractant receptor-homologous molecule expressed on T_H2 cells is expressed on T_H2 cells, ILC2s, eosinophils, basophils, and airway epithelial cells.⁶⁸ Signaling via this receptor mediates migration of T_H2 cells, ILC2s, eosinophils, and basophils, stimulates the production of T₂ cytokines, and promotes migration and differentiation of airway epithelial cells.⁴⁹ Its ligand, prostaglandin D₂, is elevated in bronchoalveolar lavage fluid from patients with severe asthma and the number of DP₂-positive cells increases with asthma severity.^{49,69} Thus, prostaglandin D₂ may be an important mediator of severe asthma. To the authors' knowledge, no studies of biologics against this target have been published. However, early studies of 2 oral DP₂ inhibitors demonstrated efficacy in reducing allergen-induced late-phase asthmatic responses in subjects with mild, steroid-naïve asthma.^{70,71} A small study examining the oral DP₂ antagonist fevipiprant in 61 subjects with persistent, moderate-to-severe eosinophilic asthma (>90% Global Initiative for Asthma treatment step 4 or 5) demonstrated a favorable safety profile and significantly decreased eosinophilic airway inflammation and epithelial damage parameters. Although asthma quality-of-life scores significantly improved, FEV₁ did not.⁷² Another orally administered DP₂ inhibitor, OC000459, did demonstrate significant and clinically meaningful improvements in FEV₁ in patients with an eosinophilic phenotype.⁷³ Larger

and longer-term studies are needed to evaluate the clinical efficacy of DP₂ inhibitory strategies for persistent asthma.

Targeting epithelial-derived alarmins

In addition to providing a physical barrier, lung epithelial cells produce mediators and cytokines that propagate innate and adaptive immune responses.⁷⁴ These include the "alarmin" cytokines, TSLP, IL-25, and IL-33, which promote the differentiation and activation of T_H2 cells and ILC2s.^{74,75} TSLP is produced in high amounts by lung epithelial cells following contact with cysteine protease-containing allergens, such as the major house dust mite allergen Der p1. In addition, TSLP promotes activation of mast cells, basophils, and dendritic cells. TSLP-activated dendritic cells prime naïve T cells to differentiate into T_H2 cells.⁷⁶ A human anti-TSLP mAb, AMG 157, significantly reduced early and late-phase allergen-induced bronchoconstriction and parameters of allergic airway inflammation in a trial of 31 subjects with mild allergic asthma.²³ The therapeutic efficacies of blockades of IL-25, IL-33, or their respective receptors still need to be established.

CONCLUSIONS

The landscape of biologic therapies for severe asthma is expanding. Several mAbs or antisense inhibitors are available or under development for T₂ high asthma, including those targeting IgE, IL-5, IL-4, IL-13, GATA-3, and TSLP (Table 1). Treatment options remain limited for T₂ low asthma despite early attempts at targeting T₂ low pathways. In the United States and Europe, omalizumab, mepolizumab, and reslizumab are commercially available for the treatment of inadequately controlled asthma in subjects with T₂ high biomarkers. Other biologics, including benralizumab and dupilumab, are in late stages of clinical development. Despite the growing repertoire of biologic therapies, uncertainties regarding their use in severe asthma exist and deserve further research. The optimal treatment duration, approach to discontinuation, and ability or lack thereof to modify disease progression need to be better characterized for each biologic. In addition, the use of biologics for the treatment of asthma in special populations, such as young children or those with associated comorbidities, for example, rhinosinusitis with nasal polyposis or atopic dermatitis, is not well defined. The safety and efficacy of administering more than 1 biologic in combination is also an area for future research. Last, improved biomarkers are needed to guide treatment decisions in subjects with both T₂ high and especially T₂ low asthma.

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