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REVIEW

Asthma Biologics Across the T2 Spectrum of Inflammation in Severe Asthma: Biomarkers and Mechanism of Action

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Abstract: Airway inflammation, a hallmark feature of asthma, drives many canonical features of the disease, including airflow limitation, mucus plugging, airway remodeling, and hyperresponsiveness. The T2 inflammatory paradigm is firmly established as the dominant mechanism of asthma pathogenesis, largely due to the success of inhaled corticosteroids and biologic therapies targeting components of the T2 pathway, including IL-4, IL-5, IL-13, and thymic stromal lymphopoietin (TSLP). However, up to 30% of patients may lack signatures of meaningful T2 inflammation (ie, T2 low). In T2-low asthma patients, T2 inflammation may be masked due to anti-inflammatory treatments or may be highly variable depending on exposure to common asthma triggers such as allergens, respiratory infections, and smoke or pollution. The epithelium and epithelial cytokines (TSLP, IL-33) are increasingly recognized as upstream drivers of canonical T2 pathways and as modulators of various effector cells, including mast cells, eosinophils, and neutrophils, which impact the pathological manifestations of airway smooth muscle hypertrophy, hypercontractility, and airway hyperresponsiveness. Approved biologics for severe asthma target several distinct mechanisms of action, leading to differential effects on the spectrum of T2 inflammation, inflammatory biomarkers, and treatment efficacy (reducing asthma exacerbations, improving lung function, and diminishing symptoms). The approved anti-asthma biologics primarily target T2 immune pathways, with little evidence suggesting a benefit of targeting non-T2 asthma-associated mediators. Indeed, many negative results challenge current assumptions about the etiology of non-T2 asthma and raise doubts about the viability of targeting popular alternative inflammatory pathways, such as T17. Novel data have emerged from the use of biologics to treat various inflammatory mediators and have furthered our understanding of pathogenic mechanisms that drive asthma. This review discusses inflammatory pathways that contribute to asthma, quantitatively outlines effects of available biologics on biomarkers, and summarizes data and challenges from clinical trials that address non-T2 mechanisms of asthma.

Keywords: thymic stromal lymphopoietin, TSLP, T2 inflammation, asthma, biologics, biomarker, anti-TSLP

Introduction

Asthma is a chronic inflammatory airway disease that affects approximately 350 million people globally.[1] Severe asthma occurs in 5% to 10% of all asthma patients[2] and in the US, approximately 20% to 50% of severe asthma patients have uncontrolled disease, and may not experience appropriate escalation of care in the form of specialist visits and medication escalation.[3]

Airway inflammation is a hallmark feature of asthma and underscores the canonical features of the disease, including airflow limitation, mucus plugging, and airway remodeling and hyperresponsiveness. A central challenge in the management of severe asthma is the heterogeneity of the disease, as the majority of patients have multiple drivers of inflammation that are not fixed and can evolve over time in response to environmental triggers (eg, viruses, allergens, cigarette smoke, pollutants, etc), age, and treatment. Variable responses to medication use and the presence of comorbidities also contribute to the difficulty in managing asthma.[4–6]

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Since the first biologic therapy, omalizumab, was approved for the treatment of moderate-to-severe allergic asthma over 20 years ago, significant progress has been made in understanding of how blocking specific immune pathways influences clinical outcomes and may modify the course of disease. Until recently, all of the approved biologics were restricted to patients with allergic and/or eosinophilic asthma, corresponding to the well-described biological phenotype of type 2 (T2)-high asthma driven by immunoglobulin E (IgE, targeted with omalizumab) and/or interleukin (IL)-5/IL-5 receptor (IL-5R; targeted with mepolizumab, reslizumab, and benralizumab), and/or IL-4 and IL-13 (targeted through IL-4R with dupilumab).[4–7]

Less is known about the key pathologic drivers of what has been described as T2-low and non-T2 asthma, where patients often present with higher symptom burden, may be refractory to inhaled corticosteroid (ICS) therapy, have oral corticosteroid (OCS) resistance, and have higher healthcare utilization.[8] Low T2 asthma can be defined as low levels of T2 biomarkers (eosinophils, fractional exhaled nitric oxide [FeNO], and IgE), resulting from a combination of variable exposure to asthma triggers, masking of inflammation due to anti-inflammatory treatments, and alternative disease processes, such as airway remodeling, airway hyperresponsiveness (AHR), and anatomical pathology due to underlying obesity and metabolic dysfunction. The remaining unmet need for additional effective therapeutic options in non-T2 asthma is not from lack of clinical investigation or pharmaceutical investment. Numerous molecules targeting components of non-T2 pathways, eg, those driving neutrophilic or mixed granulocytic inflammation, have not demonstrated sufficient clinical benefit over placebo for requisite approval.

The advent of a novel therapy, tezepelumab, approved in 2021 by the US Food and Drug Administration, introduced the first multipathway targeting biologic that was not restricted by phenotypes or biomarkers.[9] Tezepelumab targets the epithelial cytokine thymic stromal lymphopoietin (TSLP), which is upstream in the inflammatory cascade and is involved in both the initiation and persistence of airway inflammation in asthma. Evidence from randomized controlled trials has demonstrated clinical benefit with tezepelumab in both T2-high and T2-low asthma.[10,11] Consistent with T2-high effects, tezepelumab down-regulates downstream components of the inflammatory cascade, including IL-4, IL-5, IL-13, and a range of other T2 biomarkers, with corresponding declines in FeNO, serum IgE, and blood and airway eosinophil counts, as well as reductions in mucus plug scores.[12–17] Beyond canonical T2 effects, tezepelumab has also consistently reduced AHR in placebo-controlled studies, likely via mast cell and airway smooth muscle effects.[14,15]

In this review, we characterize the spectrum of inflammation contributing to the pathophysiology of severe asthma, present and compare evidence for the T2-targeted or "T2-and-beyond" effects of current asthma biologics,[18] and summarize the challenges in targeting non-T2 mechanisms from unsuccessful biologic clinical trials that may inform our understanding of immune modulation in severe asthma.

Section 1

The Spectrum of Inflammatory Pathways in Severe Asthma

The T2 inflammatory paradigm is firmly established as the dominant mechanism of asthma pathogenesis, largely due to the success of ICSs, as well as biologic therapies targeting components of the T2 pathway. Yet, signatures of T2 inflammation, including elevated blood and airway eosinophils and heightened expression of IL-4, IL-5, and IL-13, are only present in approximately 57% to 70% of patients with asthma.[19,20] Using bronchoscopy, Wenzel et al[21] found that only half of severe asthma patients had eosinophils infiltrating the bronchial mucosa, whereas the remainder did not show eosinophilic inflammation despite similar reductions in lung function. At the gene expression level, approximately half of patients with asthma show an IL-13-inducible gene signature in the bronchial epithelium, with the other half indistinguishable from controls; notably, only patients with this T2 gene signature responded favorably to ICS treatment as measured by improvement in forced expiratory volume in one second (FEV_1).[22] Data from this study helped molecularly define T-helper type 2 (Th2) asthma as the dominant asthma phenotype (now known widely as "T2 asthma").

Generally, asthma patients receive ICS per treatment guidelines[2] or ICS+OCS to help control exacerbations and prevent hospitalizations, with both approaches resulting in a reduction in some T2 biomarker levels (eg, FeNO), making phenotyping more challenging.[23,24] Patients with asthma report numerous triggers for symptoms and exacerbations. In one study, the median trigger number per patient was 8, with the most frequent triggers being weather or air changes, viral infections, seasonal allergies, perennial allergies, and exercise.[25] Higher numbers of triggers are associated with

greater uncontrolled disease burden.[25] Given these triggers interact with the airway epithelium to drive a range of downstream inflammatory responses, including allergic and nonallergic immune pathways,[26] the measure of T2 inflammation at a given timepoint may be highly variable. Together, these findings suggest that inflammation in asthma is a continuous spectrum and T2-low asthma is a heterogeneous phenotype, likely driven by both underlying non-T2 biological pathways and reciprocal T2 repression by T1/T17 pathways (in combination with pharmacologically suppressed T2 inflammation in some patients; Figure 1).[27]

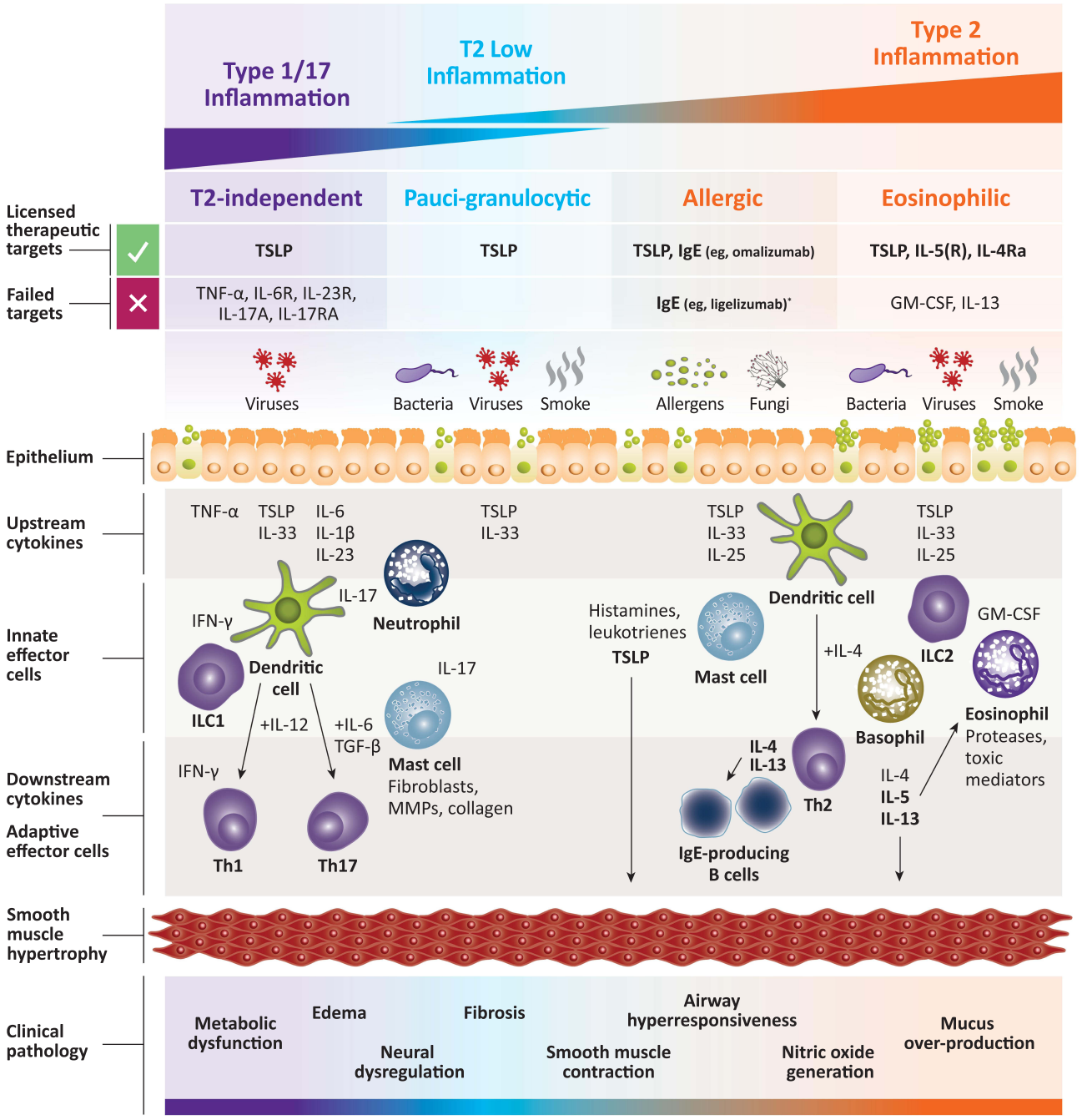

Figure 1 The spectrum of inflammatory pathways in asthma spans across T2 inflammation (allergic/eosinophilic) to T2-low inflammation (pauci-granulocytic and lower levels of allergic or eosinophilic) to Type 1/17 inflammation (neutrophilic). While the mixed immune responses (T2, T17, T1, innate) associated with asthma emphasize the disease heterogeneity, only biologic therapies with some degree of anti-T2 activity have been successful to date. *Although ligelizumab is more potent than omalizumab at inhibiting IgE binding to the high-affinity FcεRI, there is differential IgE blocking properties relative to FcεRI and FcεRII/CD23 between the two compounds, potentially blunting the effect in asthma.[28]

Abbreviations: GM-CSF, granulocyte macrophage colony stimulating factor, Ig, immunoglobulin, IFN, interferon, IL, interleukin, MMPs, matrix metalloproteinases, T2, type 2, TGF, transforming growth factor, Th, T helper cells, TNF, tumor necrosis factor, TSLP, thymic stromal lymphopoietin.

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T2 Inflammatory Pathways in Asthma

The most well-defined immunologic pathway in asthma is the T2 immune response, driven primarily by eosinophils, mast cells, basophils, CD4+ Th2 cells, T2 innate lymphoid cells (ILC2s), and IgE-producing B cells.[22,29] The T2 process may be initiated upstream at the airway epithelium in response to inhaled aeroallergens or injury/damage, causing release of the epithelial cytokines TSLP, IL-33, and IL-25 (also known as alarmins), which in turn could activate innate immune cells such as dendritic cells (DCs), basophils, ILC2s, and mast cells to release T2 cytokines, including IL-4, IL-5, IL-9, and IL-13.[30] Activated DCs migrate from the lung to the draining lymph nodes where, in the presence of IL-4, they can initiate an adaptive Th2 response by polarizing naïve T cells to differentiate into effector Th2 cells, producing high levels of T2 cytokines.[27] Downstream T2 cytokines, IL-4 and IL-13, are the primary drivers of IgE antibody class switching in B cells and induction of high-affinity IgE, which is essential for the initiation of allergic airway inflammation. Through binding to its receptor on structural cells of the airway, IL-13 (and to a lesser extent IL-4) stimulates goblet cell metaplasia, excess mucus production, and secretion from goblet cells, while also driving production of nitric oxide and priming smooth muscle contraction, contributing to subsequent bronchial hyperresponsiveness. Increased production of IL-5 induces eosinophilia, facilitating the pathologic release of granules containing proteases and other toxic mediators into the airways.[22,31] In addition, airway epithelial cells express a functional IL-5R, suggesting that IL-5 may have direct effects on the airway epithelium, as well as disruption of epithelial integrity.[32] Clinical biomarkers for T2-high asthma, as quantitative readouts of T2 pathway activation, include elevated blood eosinophil counts with high FeNO levels, and T2-high asthma is clinically associated with allergic rhinitis, chronic rhinosinusitis with and without nasal polyps, and other ear, nose, and throat comorbidities.[33,34]

Epithelium and Epithelial Cytokines as Upstream Drivers of Inflammation: "T2 and Beyond"

The airway epithelium is both a physical barrier and a first line of defense against allergens, pathogens, and environmental toxins, as well as a key coordinator of immune responses to environmental stimuli.[35] Epithelial disruption is increasingly recognized as an early event in the pathogenesis of atopic disease, including asthma. Moreover, epithelial homeostasis becomes skewed towards impaired innate and adaptive immune responses, persistent inflammation, barrier disruption, and tissue remodeling during disease progression.[36] In asthma, immune hyperreactivity leads to excessive production and release of pro-inflammatory cytokines. In response to inhaled asthma triggers, the epithelial cytokines TSLP, IL-25, and IL-33 serve as potent upstream activators of both innate and adaptive immune responses, and elevated levels of epithelial cytokines have been found to correlate with T2 inflammation and disease severity.[30] Increasing evidence positions the epithelial cytokines as upstream drivers of not only canonical T2 pathways, but also those driven by a variety of effector cells, including mast cells, eosinophils, and neutrophils, to impact the pathological manifestations of airway smooth muscle hypertrophy, hypercontractility, and AHR.

IL-25, a member of the IL-17 family of cytokines, is constitutively expressed in tuft cells within the bronchial epithelium for immediate secretion upon exposure to proteases or pathogens. IL-25 signals through an IL-17RA/IL-17RB heterodimeric receptor and activates ILC2s and Th2 cells to produce IL-5 and IL-13, promoting T2 inflammation.[37]

IL-33, a member of the IL-1 family, is constitutively expressed in barrier epithelial cells, predominantly basal cells, but lacks a secretory signal motif and is tightly sequestered in the cell nucleus bound to chromatin. IL-33 is passively released upon tissue injury or necrosis as a result of exposure to cigarette smoke, pollutants, and viruses or bacteria. Proteolytic activation of IL-33 by allergens or proteases is required for binding to its receptor, ST2 (also known as IL-1 receptor-like 1), expressed on multiple cell types, including airway endothelial cells, ILC2s, mast cells, and Th cells (both Th1 and Th2).[38] IL-33 in its oxidized form was also recently discovered to signal through the RAGE/EGFR pathway, independently of ST2.[39] In addition to stimulating production of IL-4, IL-5, and IL-13, and promoting eosinophilic T2 inflammation, IL-33 may amplify the T1 inflammatory response to viral infections together with IL-12 to stimulate natural killer (NK) cells, NK T cells, ILC1s, and Th1 cells to produce IFNγ.[40] An IL-33-activating mast cell signature was also found to be enriched in the sputum of severe asthma patients with a mixed granulocytic and neutrophilic phenotype.[41]

TSLP, a member of the IL-2 family, is actively secreted by airway epithelial cells and immune cells, such as DCs, stromal cells, basophils, and mast cells, upon exposure to respiratory viruses, air pollutants, allergens, and other stimuli.[42] TSLP can activate the innate T2 pathway through ILC2s, as well as the adaptive T2 pathway through Th2 cells, with both leading to the production of IL-4, IL-5, and IL-13. In response to TSLP, DCs induce naïve CD4+ T-cell proliferation and Th2 differentiation via upregulation of OX40L. TSLP-activated DCs can prime CD4+ T cells in an antigen-specific manner and further differentiate Th2 memory cells.[43] Beyond T2 inflammation, TSLP may help facilitate the recruitment of inflammatory T1 cells through the Th1 chemokines CXCL10 and CXCL11,[44] and TSLP signaling together with Toll-like receptor 3 can promote differentiation of Th17 cells via DCs.[45] TSLP is involved in mast cell development by prolonging mast-cell survival and interfering with apoptosis,[46] as well as synergizing with neuropeptides such as substance P and pro-inflammatory cytokines such as IL-1B to promote degranulation of mast cells and production of cytokines and chemokines. Moreover, TSLP has been shown to directly activate sensory neurons in both T2 and non-T2 conditions, inducing itch in the skin.[47]

T2-Low Inflammation: a Role for Other Pathways?

While the search for predictive genetic and inflammatory T2-low asthma markers continues,[48] to date these patients are identified merely by the absence of a prominent T2 immune profile, rather than by the presence of a specific alternative set of pathologically-relevant immune markers. Unfortunately, the T2-low asthma phenotype has no clear consensus definition and no alternative biomarkers whose presence (rather than absence) identifies asthmatic subjects whose respiratory disease is: 1) etiologically similar, and 2) distinct from T2-driven disease (although some T2-low phenotypic subtypes have been proposed, eg, obesity-driven, neutrophilic, etc). In contrast to the dichotomous T2-high vs T2-low paradigm, inflammation in asthma can also be described as existing along a T2 continuum. T2 mediators (such as eosinophils) are not entirely absent in the airways of patients with T2-low status, but whether they play a pathologic role in T2-low asthma is unclear.

T2-low inflammation in asthma is not well understood and has been linked to the activation of T1 and/or T17 responses and the presence or absence of granulocytes, including neutrophils (mixed granulocytic or pauci-granulocytic phenotype, respectively).[49] It has been known for many years that moderate-to-severe asthma patients have complex granulocytic inflammation of the airways, which is more notable in those who are poorly responsive to corticosteroids.[50] The functional significance of this non-T2 inflammation remains a topic of significant debate. While it is true that corticosteroids, particularly OCS, mask T2 inflammation due to their effects on eosinophilic apoptosis and prolonging neutrophilic survival, among other mechanisms, a role for T1/T17 pathways, albeit not causal, is suggested by observations that airway non-T2 cytokines are elevated in symptomatic asthma at the time of exacerbation and that non-T2 inflammation can be present in patients who are steroid-naïve.[51,52] Clinically, noneosinophilic or T2-low asthma has been associated with obesity, smoking, and disease onset after 50 years of age. Obesity has been associated with chronic low-grade inflammation and production of the inflammatory mediators tumor necrosis factor (TNF)-α, IL-6, and C-reactive protein, and in asthma, studies have demonstrated a reduction in sputum eosinophils, but an increase in sputum neutrophils, with increasing body mass index.[53,54]

T1 Immune Response

The conventional view of the T1 immune response is a mutually antagonistic relationship with T2 pathways, where DCs activated in response to viral infection or signaling through IL-12 drive the differentiation of CD4+ Th1 cells or cytotoxic CD8+ T cells, producing large amounts of IFNγ that directly antagonizes IL-4 and the T2 response.[27] In reciprocal fashion, eosinophils and IgE have been shown to suppress anti-viral IFNα secretion from plasmacytoid DCs.[55] Serum levels of IFNγ have been found to be positively correlated with AHR in patients with allergic asthma and increased numbers of virus-specific Th1 cells have been associated with worse lung function in asthmatics.[56] However, the T1 and T2 pathways are likely much more plastic than previously thought. In a mouse model of acute eosinophilic airway inflammation, Th1 cells were shown to support the accumulation of Th2 cells in the lung, and in another study, virus-specific T1 cells were shown to drive the recruitment of resting T2 cells, suggesting cooperation between the T1 and T2 pathways.[57,58]

Th17 Immune Response

Th17 immunity supports and facilitates immune responses to extracellular bacterial and fungal pathogens, especially at mucosal surfaces. IL-17 is produced by Th17 cells, as well as innate cells such as NK cells, and has broad inflammatory effects, most notably on neutrophil recruitment and activation.[59] The signals leading to T17 inflammation and Th17 differentiation are complex and include the combination of IL-6 and transforming growth factor-B, as well as IL-1B, IL-21, and IL-23.[27] Several common aeroallergens, including house dust mite and pollen, can stimulate the production of IL-6 by airway epithelial cells, and exposure to air pollution and particulate matter has been shown to promote Th17 differentiation and aggravate asthma.[60,61] There is also a complex relationship between T2 and T17 inflammation in asthma, where IL-17 is known to be produced by Th2 cells with the capacity to simultaneously produce both IL-4 and IL-17 during the chronic stage of asthma. Of note, cells expressing both T2 and T17 cytokines have been described in airway samples from asthma patients with more severe disease.[62]

Section 2

Clinical Efficacy of Biologics in Severe Asthma and Relation to T2 Inflammation

Biologic therapies for severe asthma improve disease control through specific blockade of molecular targets involved in asthma inflammation. Most biologics target downstream components of the inflammatory cascade, including IgE (omalizumab), IL-5 (both mepolizumab and reslizumab), IL-5R (benralizumab, leading to eosinophil depletion), and IL-4Ra (dupilumab, leading to blockade of IL-4 and IL-13 activity), while the most recently approved biologic, tezepelumab, targets the upstream epithelial cytokine TSLP (Figure 1).[4–7,9] Given these biologics have different mechanisms of action, they show differential effects on the spectrum of T2/non-T2 inflammation, inflammatory biomarkers, and the pathophysiology of asthma, resulting in differential efficacy for patients in reducing asthma exacerbations.

Clinical Effect by Baseline Patient Characteristics

Blood Eosinophil Count

Randomized controlled trials in patients with severe asthma have shown that the efficacy of all biologics in reducing the annualized asthma exacerbation rate (AAER) increases with higher baseline blood eosinophil counts (BEC ≥150 cells/μL,[12,63–67] ≥300 cells/μL,[12,63,64,68–73] or ≥450 cells/μL[12,64,74–76]). In patients with baseline BEC ≥300 cells/μL, efficacy in AAER reduction vs placebo was demonstrated in all trials where this subgroup was reported;[12,63,64,68–76] the greatest reductions (≥60%) were observed with dupilumab and tezepelumab.[12,64,70] In patients with BEC 150 to <300 cells/μL, AAER reduction was only demonstrated consistently with tezepelumab,[12,64] although one study reported this finding for dupilumab (300- mg dose only).[70] In patients with BEC <150 cells/μL, tezepelumab uniquely demonstrated efficacy in exacerbation reduction, including those exacerbations associated with hospitalization or an emergency room visit.[10]

Allergic Status

Allergic asthma is typically defined by sensitization to a perennial aeroallergen and is associated with elevated serum IgE levels.[77] While atopy is relatively common in severe asthma, measurement of IgE has not been useful in predicting response to any biologic, including omalizumab,[78] nor is there an association between increasing IgE level and increased risk for exacerbation. In fact, an inverse relationship between serum IgE level and risk for exacerbations was observed (ie, higher exacerbation rates in patients with lower IgE levels), whereas a direct or positive relationship was observed between increasing FeNO and BEC levels.[79] The pooled NAVIGATOR study also found increasing risk of exacerbations in placebo-treated patients with increasing baseline levels of FeNO or BEC, whereas there was no relationship between increasing baseline IgE levels and risk for exacerbation.[10] Oppenheimer et al[80] reported that IgE, when used in allergic asthma, was not a predictive biomarker of treatment response to any biologic for severe asthma, whereas BEC, as an indicator of an eosinophilic phenotype, had utility in this regard. Finally, although long-term use of omalizumab has been

shown to decrease IgE levels,[81] its use in the EXTRA study resulted in only a modest reduction in exacerbations (~25%).[82]

According to the International Severe Asthma Registry, a large proportion of adults with severe asthma have both elevated serum total IgE levels and elevated BECs,[83] resulting in an allergic and eosinophilic phenotype. In a literature review of phase 3 randomized controlled trial data,[84] among patients with allergic severe asthma and BECs ≥260 cells/μL or ≥300 cells/μL, the smallest AAER reduction (25% to 32%) was observed with omalizumab[69,82] and the greatest AAER reduction (60%) was observed with tezepelumab.[10,12] In patients with allergic severe asthma and BECs ranging from <150 cells/μL to <300 cells/μL, tezepelumab was associated with a clinically meaningful AAER reduction of 45% to 59%,[10,12] which was not observed with benralizumab and omalizumab (26% and 9%, respectively);[69,85] data for mepolizumab and dupilumab were not available for analysis.

Baseline Fractional Exhaled Nitric Oxide Levels

Fractional exhaled nitric oxide, a quantitative biomarker and noninvasive easily administered breathalyzer test, is also linked to mechanisms involved in T2 inflammation.[86] IL-13 signalling stimulates the production of the enzyme inducible nitric oxide synthase by airway epithelial cells, resulting in an increase in FeNO, thus making FeNO a surrogate biomarker for IL-13-mediated inflammation.[86] FeNO levels >50 ppb in adults suggest eosinophilic airway inflammation and excessive IL-13 signalling, as the inducible nitric oxide synthase enzyme responsive for generating airway nitric oxide is regulated by IL-13.[86]

Inconsistent findings in changes to FeNO levels and prediction of treatment response in patients with allergic asthma have been reported for omalizumab;[69,87] thus, the role of FeNO as a biomarker for omalizumab response remains unclear. Studies with mepolizumab and benralizumab show that despite reduced acute exacerbation rates, there was no significant decline in FeNO levels nor did FeNO levels predict treatment response.[73,88] However, elevated levels of FeNO were associated with increased risk of exacerbations as shown in a dupilumab placebo-controlled study.[63,89] Overall, US-approved injectable biologics that inhibit IgE and anti-IL-5 agents that act on eosinophils have inconsistently been shown to impact FeNO levels. Nevertheless, tezepelumab and dupilumab have been associated with significant reductions in AAER and improved lung function in patients with high baseline FeNO levels,[10,12,63] likely secondary to their attenuation of IL-13 signalling. Notably, FeNO is a predictor of response independent of BEC for dupilumab.[89]

Airway Hyperresponsiveness

Airway hyperresponsiveness is a cardinal feature of asthma and is defined as the heightened responsiveness to inhaled bronchoconstrictors and/or the increased production of mediators of bronchoconstriction following inhalation of allergic, irritant, or osmotic compounds.[90] AHR is associated with instability of the airway smooth muscle, infiltration of inflammatory cells such as mast cells, and in some patients with baseline airflow obstruction.[90] Bronchoprovocation testing to measure AHR is conducted using either direct challenge agents, such as methacholine, or indirect agents, such as mannitol (osmotic challenge) or allergen-specific challenge in patients with allergic sensitization. Allergen challenge is used to assess both the early allergic response (EAR), which develops within the first 15 minutes of allergen administration, and the late allergic response (LAR), which develops 3–4 hours after allergen challenge and is associated with an influx of cellular inflammation. In a systematic review of randomized, placebo-controlled trials of both approved and non-approved biologics, tezepelumab was the only marketed biologic to demonstrate reductions in EAR and LAR, in addition to attenuating the accompanying increase in nonspecific AHR.[91] Omalizumab reduced AHR to methacholine, acetylcholine or adenosine monophosphate in 3 of 9 studies; reductions in EAR (4/5 studies) and LAR (2/3 studies) were also observed. Mepolizumab has not been shown to affect AHR (3/3 studies), as well as EAR and LAR (1 study). Tezepelumab reduced AHR to methacholine or mannitol in 3 of 3 studies, and reduced EAR and LAR in 1 study. No dupilumab or reslizumab studies were identified. These findings suggest that inhibition of T2-specific pathways alone, with therapeutics targeting eosinophils or IL-4/IL13, is not sufficient to meaningfully impact AHR and that inhibition of mast cell activation appears to be necessary, with agents targeting TSLP or IgE. The effect of tezepelumab on AHR could explain, at least in part, the reduction in exacerbation rates observed in patients with T2-low asthma.

Mucus Plugging

Airway mucus plugs are present and persistent in most patients with severe asthma and are associated with more severe disease and greater lung function deficit.[92] Mucus plugs develop from T2 inflammation, where IL-13 promotes mucin production and IL-5 leads to eosinophil-mediated oxidation of the mucin.[93] In randomized, placebo-controlled trials, tezepelumab and dupilumab have both been shown to reduce mucus plugging vs placebo.[17,94] The dupilumab VESTIGE study included patients with elevated T2 biomarkers (BEC ≥300 cells/μL and FeNO ≥25 ppb) and showed significantly greater reductions in mucus plug score for dupilumab vs placebo alongside improved lung volumes distal to the resolved mucus plug.[94] The tezepelumab CASCADE study, in contrast to the dupilumab study, included patients with a greater range of BEC (25% BEC <150 cells/μL; ~40% BEC 150–300 cells/μL; and ~35% BEC ≥300 cells/μL).[15] In tezepelumab recipients, reductions in mucus plug scores were correlated with improvements in lung function and reductions in BEC and levels of eosinophil-derived neurotoxin, a biomarker of eosinophilic degranulation.[17] A subgroup analysis of patients from CASCADE with elevated BEC ≥300 cells/μL and FeNO ≥25 ppb demonstrated a greater numeric reduction in mucus plug scores from baseline.[17]

Biomarkers Used to Assess Severe Asthma

Clinical biomarkers are now commonly used in patients with severe asthma not only to identify individual phenotype, but also to predict and/or prevent disease risk/severity/prognosis, acute exacerbations of asthma, and likelihood of response to treatment.[33] Biomarker profiling may also assist in identifying patients with subclinical airway inflammation or disease who may be at risk of progressing to airflow restriction.[95] The most widely used biomarkers in clinical practice include BEC, FeNO, and serum total IgE.[33] A plethora of research-focused and emerging novel biomarkers, such as IL-5, IL-13, periostin, IL-6, IL-17, IL-22, thymus and activation-regulated chemokine (TARC)/CCL17, matrix metalloproteinases, eotaxin-1 and −3, and eosinophil-derived neurotoxin,[96–100] may be used in the future to further classify clinical phenotypes and guide treatment. While some cytokines have a clear association with asthma pathogenesis, not all of these molecules are practical biomarkers because of the low levels of these molecules in accessible bodily fluids (such as IL-4, TSLP, etc) and/or technical limitations with their detection.

Imaging is a new noninvasive biomarker frontier that can reveal air trapping, presence of mucus plugs, evidence of increased work of breathing, and airflow obstruction.[101,102] Imaging in severe asthma predominantly uses computed tomography and magnetic resonance imaging to characterize the type, extent, and severity of disease. New techniques, including the use of hyperpolarized noble gases (^{3}He, ^{129}Xe) as airway tracers[103] and morphometric analysis of extrapulmonary skeletal and support tissue,[104] are providing a more complete picture of the dynamic and regional effects of asthma on pulmonary function. In the future, computed tomography imaging may play an important role in identifying unique clusters of asthmatic patients and helping to guide treatment in real-world practice.

Effects of Biologics on Biomarkers of Type 2 Inflammation

The last two decades have witnessed the advent of highly effective therapies, which target a variety of biomarkers associated with airway inflammation across the T2 spectrum (Figure 1). Few studies have quantified the effects of available biologics on the wide range of biomarkers used to assess severe asthma. To address this gap, a descriptive search of published randomized, placebo-controlled trials of biologics (omalizumab, mepolizumab, benralizumab, dupilumab, and tezepelumab) in adolescent and adult patients with any type or severity of asthma that evaluated biomarkers of T2 inflammation in asthma was performed.[105] The biomarkers evaluated included eosinophils (blood/peripheral/circulating/tissue/submucosal/sputum), FeNO, and IgE, as well as any cytokine or chemokine assessments. Study designs, patient demographics, and clinical characteristics are presented in Supplementary Table 1, and a more detailed summary of biomarker changes for each biologic is provided in Supplementary Table 2.

Table 1 presents the effects of biologics by pathway (IL-5, IL-4/IL-13 pathways), with up/down arrows indicating reductions or increases in biomarker level (eg, 1 arrow = 5% to 20%, 5 arrows = >80% change in biomarker status). Table 2 presents directional changes in biomarkers by individual biologic. Benralizumab[68,71] and mepolizumab[67,73,106] had the largest impact on the IL-5 pathway, with complete or nearly complete reductions in circulating blood eosinophils (Table 1). Reductions in sputum[106,107] and tissue eosinophils[107,108] were also noted, but the magnitude of the reductions was not as great as those of blood eosinophils. Neither anti-IL-5/IL-5R agent impacted the IL-4/IL-13

Table 1 Effects of Biologics on Biomarkers of Type 2 Inflammation in Asthma

Biomarker Changes From Baseline					
Biomarker (Mean or Median* Change From Baseline: Active vs Placebo)	**Omalizumab in Allergic Asthma**	**Mepolizumab in Eosinophilic Asthma**	**Benralizumab in Eosinophilic Asthma**	**Dupilumab in All Asthma Phenotypes**	**Tezepelumab in All Asthma Phenotypes**
BEC	−4.0% vs +23.1%[113] −13.1% vs 0%[3]	−86.0%[106]	−89.0% vs +17.7%[68] −92.7% vs +6.9%[71] −89.9% vs +11.9%[109]	**300 mg**: +43.8% vs +33.6%[120]	−44.4% vs −5.2%[119] *−50.0% vs −3.0%[118]
FeNO	−4.2 ppb[82] −11.1% vs 0%[112]	−3.0%[73]	+4.9 vs −0.5 ppb[109] +5.4%	**200 mg**: −27.4% vs +5.3%[63] **300 mg**: −25.6% vs +1.3%[63]	−36.7% vs −8.9%[119] *−25.2% vs 0%[119]
IgE	−89–99% in free IgE[121]	NR	NR	**300 mg**: −58.4% vs +9.9%[120]	−33.2% vs −4.5%[119] *−20.1% vs −1.4%[118]
IL−5	NR	NR	**Phase 1–200 mg**: +284% vs −64%[110] **Phase 2–200 mg**: +250% vs 0%[110]	NR	−61.8% vs −13.4%[119] *−60.0% vs +2.8%[118]
IL−13	−19.2% vs −12.7%[112]	NR	NR	NR	−51.1% vs −10.0%[119] *−51.6% vs −1.5%[118]
TARC	NR	NR	NR	**300 mg**: −22.7% vs +25.9%[120]	*−19.0% vs −6.7%[118]
Periostin	NR	NR	NR	**300 mg**: −17.8% vs −2.4%[120]	*−13.6% vs −5.4%[118]
Eotaxin−1, eotaxin−3	NR	NR	**Phase 1–200 mg**: +85.2% vs +11.8%[110] **Phase 2–200 mg**: +103.5% vs −16.1%[110]	**300 mg**: −21.0% vs +57.3%[120]	NR
Sputum eosinophils	−27%[114] −106%[115]	−32.0%[73]	**Pooled 100 mg and 200 mg**: *−89.9% vs −66.6%[107]	Absolute change −2.9% vs +5.0% Median difference −7.9%[117]	**700 mg IV**: −69.0% vs +26.0%[14]
Tissue eosinophils	−81%[114] −75%[115]	−55.0%[67] −59.0% vs −15.0%[108]	**Pooled 100 mg and 200 mg**: *−95.8% vs −46.7%[107]	−6.0 vs 5.8 cells/mm^2[2,116]	−74.0% vs +28.0%[14] −89.0%[15]

Notes: Data shown are for approved dose unless data for the approved doses were not reported. Results represent means: medians* were used when means were not reported. When multiple results were available with the approved dose, each result is shown on a separate line. Color shading key: yellow = clear (>20%) reduction, blue = uncertain (≤20%) reduction, pink = no reduction/increase.

Abbreviations: BEC, blood eosinophil count; FeNO, fractionated exhaled nitric oxide; IgE, immunoglobulin E; IL-5, interleukin 5, IL-13, interleukin 13; NR, not reported; ppb, parts per billion; TARC, thymus and activation-regulated chemokine.

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Table 2 Directional Changes in Biomarkers Organized by Type 2 Inflammatory Pathways

Directional Changes in Biomarkers Organized by Type 2 Inflammatory Pathways: Effect on IL-5 Pathway				
Biologic	**Serum IL-5**	**Blood eosinophils**	**Sputum eosinophils**	**Tissue eosinophils**
Omalizumab	NR	↓	↓↓↓↓	↓↓↓↓
Mepolizumab	NR	↓↓↓↓↓	↓↓↓	↓↓↓
Benralizumab	↑↑↑↑	↓↓↓↓↓	↓↓↓	↓↓↓
Dupilumab	NR	↑	↓	↔
Tezepelumab	↓↓↓	↓↓↓	↓↓↓↓	↓↓↓↓

Directional Changes in Biomarkers Organized by Type 2 Inflammatory Pathways: Effect on IL-4 and IL-13 Pathways						
Biologic	**Serum IL-13**	**FeNO**	**Periostin**	**TARC**	**Eotaxin**	**Serum IgE**
Omalizumab	↓	↓	NR	NR	NR	↓↓↓↓↓
Mepolizumab	NR	↓	NR	NR	NR	NR
Benralizumab	NR	↑	NR	NR	↑↑↑↑↑	NR
Dupilumab	NR	↓↓	↓	↓↓	↓↓	↓↓↓
Tezepelumab	↓↓↓	↓↓	↓	↓	NR	↓↓

Notes: ↑ = increase (↑ = 0 to 20%, ↑↑ = 21 to 40%, ↑↑↑ = 41 to 60%, ↑↑↑↑ = 61 to 80%, ↑↑↑↑↑ ≥81% increase); ↓ = decrease (↓ = 0 to 20%, ↓↓ = 21 to 40%, ↓↓↓ = 41 to 60%, ↓↓↓↓ = 61 to 80%, ↓↓↓↓↓ ≥81% decrease); ↔ = no change.
Abbreviations: FeNO, fractionated exhaled nitric oxide; IgE, immunoglobulin E; IL-5, interleukin 5, IL-13, interleukin 13; NR, not reported; TARC, thymus and activation-regulated chemokine.

pathway. Mepolizumab resulted in a slight reduction,[73,106] while benralizumab resulted in a slight increase in FeNO levels.[109] Neither agent reported an effect on serum IgE. Benralizumab was associated with significant increases in serum IL-5 and eotaxin-1 levels,[110] while this was not reported with mepolizumab. Omalizumab had the greatest impact on IgE, with over 90% binding of free IgE.[111] Small reductions in FeNO,[82,112] IL-13,[112] and blood eosinophils[113] were also reported, while omalizumab resulted in significant reductions in both sputum and tissue eosinophils.[114,115] Dupilumab impacted the IL-4/IL-13 pathways, with reductions in serum IgE, TARC, FeNO, periostin, and eotaxin-3,[63] while having little impact on the IL-5 pathway. Dupilumab was associated with a modest increase in blood eosinophils[63] and no change in tissue eosinophils,[116] while reducing sputum eosinophils.[117] Tezepelumab impacted both the IL-4/IL-13 and IL-5 pathways with reductions in FeNO,[12,118,119] IL-13,[118,119] TARC,[118] periostin,[118] serum IL-5,[118,119] and circulating[12,118,119] sputum[14] and tissue eosinophils.[14,15] Notably, greater reductions in eosinophils were seen in the airway (sputum and tissue) compared to the periphery (blood eosinophils). The largest number of biomarkers assessed were with tezepelumab (9 biomarkers, with reductions in 9/9 biomarkers assessed) and dupilumab (8 biomarkers, with reductions in 6/8 biomarkers). Six biomarkers were assessed with omalizumab, which showed reductions in 6/6 biomarkers. Six biomarkers were evaluated with benralizumab (3 with associated reductions, 3 with increases), and 4 biomarkers with mepolizumab (reductions in 4/4 biomarkers).

In summary, reductions in biomarkers were largely consistent with the mechanism of action of each biologic. Tezepelumab, by acting at the airway epithelium and throughout inflammatory pathways, impacted all the biomarkers measured; dupilumab, by inhibiting both IL-4 and IL-13 signaling, impacted all associated IL-4/IL-13 biomarkers with less impact on the IL-5 pathway. Omalizumab, which acts primarily by inhibiting IgE function, was also associated with significant reductions in airway eosinophils. Benralizumab and mepolizumab effects were limited to impacting the IL-5 pathway.

Section 3

Challenges in Targeting T2-Low and Non-T2 Asthma

Over the last two decades, contemporary asthma drug discovery has largely focused on two intertwined mechanisms of asthma pathogenesis: immune dysregulation and airway dysfunction. Bolstered by the clinical success of the anti-IgE antibody omalizumab in 2003, strategies targeting pulmonary immune dysregulation have consistently yielded novel asthma therapies. Unfortunately, the counterpoints to each biologic success story are the myriad candidate biologics whose development for asthma was discontinued given insufficient efficacy, safety concerns, or both.

Although disappointing, these biologic "dead ends" are instructive, clarifying the relative clinical importance of specific mediators in specific populations at various phases of disease progression.[122] As was made clear in the prior section, asthma biomarker responses vary by the biologic in use and by patient phenotype. Clinical trial biomarker data combined with network/pathway analyses have shown that some approved asthma biologics affect multiple pathways while others just modulate one effector. To date, the approved anti-asthma biologics have primarily targeted T2 immune pathways, but this is not for lack of research targeting non-T2 asthma-associated mediators. In this section, we review select discontinued asthma biologics targeting innate immune and adaptive immune mediators. These negative results informed the studies which came after and continue to challenge current assumptions about the etiology of T2-low/non-T2 asthma (Table 3).

Innate Immune Modulators

Anti-TNF-α Biologics

Golimumab (CNTO 148), initially approved in 2009, is a human IgG1 monoclonal antibody that binds the soluble and transmembrane forms of human TNF-α, preventing binding of the cytokine to its receptors (TNFR1/p55, TNFR2/p75).[132,133] Golimumab is approved for treatment of moderate-severe rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, and ulcerative colitis.[132] TNF-α is a pro-inflammatory cytokine acting via multiple mechanisms, including promotion of leukocyte adhesion (E-selectin, intercellular adhesion molecule 1, vascular cell adhesion molecule 1), enhancing cytokine release (IL-6, IL-8, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor [GM-CSF]), and regulation of inflammatory cytotoxicity (apoptosis/necrosis).[132,134] TNF-α is secreted by many immune cells (including macrophages, lymphocytes, mast cells), and human TNF-α inhalation studies show that the cytokine can trigger bronchial hyperresponsiveness and sputum neutrophilia.[135]

Interest in anti-TNF-α biologics as potential asthma treatments triggered an initial wave of small proof-of-concept clinical trials in the mid-2000s, largely with conflicting results.[136,137] Ultimately, the best powered study (with the longest treatment and follow-up period) evaluated golimumab's efficacy and safety in a cohort of severe asthmatics.[123] This phase 2 dose-ranging, randomized, double-blind, placebo-controlled trial enrolled adult subjects who remained uncontrolled despite use of high-dose ICS and long-acting β_2-agonist (LABA) plus a history of 2 or more exacerbations in the prior year. The coprimary endpoints were change in prebronchodilator percent predicted FEV_1 from baseline and frequency of severe exacerbations (requiring systemic steroids), both evaluated after 24 weeks of treatment. Investigational drug administration continued for an additional 24 weeks (total treatment time 52 weeks) during which a steroid wean was attempted, followed by a 24-week safety follow-up period offdrug. No significant differences were recorded for either coprimary endpoint at 24 weeks, with small improvements in FEV_1 noted in all arms and no difference in the mean number of exacerbations between groups. Unfortunately, safety concerns became apparent following the 24-week database lock and study agent administration was discontinued given an unfavorable risk-benefit profile, with serious infections occurring more often in golimumab-treated subjects. Also, malignancies and an infection-associated death occurred in the golimumab-treatment arm, with no such events in the placebo arm. No additional asthma studies investigating golimumab have been reported.

Following publication of the golimumab asthma study, the results of a similar, but smaller phase 2 study investigating the safety and efficacy of the anti-TNF-α drug etanercept in moderate-severe asthma adult patients were released.[124] The

Table 3 Discontinued Asthma Biologics by Pathway and Target

Target	Biologic	Phenotype/ Pathway Targeted	Indication	Trial Type	Registration #	Population	Primary Results	Secondary Results	Safety
TNF-α[123]	Golimumab (CNTO 148)	Innate immunity	Uncontrolled severe asthma	Ph2, dose finding	NCT00207740	n=309	No significant differences were observed for the change in percent-predicted FEV_1 (LSM: PBO, 2.44 [95% CI −0.574 to 5.461]; combined 100 mg and 200 mg, 2.91 [0.696–5.116]) or severe exacerbations (mean ± SD: PBO, 0.5 ± 1.07 vs combined 100 mg and 200 mg 0.5 ± 0.97) through week 24.	No treatment effect was noted on AQLQ scores either. In a subgroup analysis of subjects with at least 1 exacerbation from baseline to week 24, golimumab was most effective in suppressing additional exacerbations in subjects with later-onset disease (>12 years) and with greater bronchodilator reversibility (>12%).	Imbalance in study agent discontinuation rates between treatment arms. Unfavorable risk-benefit profile. Serious infections occurring more often in the golimumab. 1 death and all 8 malignancies in the golimumab arms, none in PBO arm.
TNF-α[124]	Etanercept	Innate immunity	Moderate-to-severe persistent asthma	Ph2	NCT00141791	n=132	No significant differences were observed between ETN and PBO for any of the efficacy endpoints. Primary endpoint was the change from baseline PBO-FEV_1% predicted at 12 wks. Secondary endpoints: morning PEF, ACQ5, asthma exacerbations, PC20 MCCT, and AQLQ.	Key secondary endpoints included ACQ-5 and AQLQ at 12 weeks. No significant differences between ETN and PBO were noted for any secondary endpoints.	

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GM-CSF[125]	Lenzilumab (KB003)	Innate immunity	Uncontrolled moderate-severe asthma (uncontrolled despite ICS/ LABA therapy)	Ph2	NCT01603277	n=129	FEV_1 at week 24 improved to 118 mL compared with 54 mL in the PBO group (p=0.224). FEV_1 improvement better in BEC >300 cohort (253 mL vs 26 mL p=0.02). There were no effects on asthma control or exacerbation rates.	Key secondary endpoints included mean cumulative asthma exacerbations at week 24 (defined as use of systemic steroids for 3 days and/or ED/ hospitalization for worsening symptoms), change in asthma symptom score, and change in ACQ-5. No drug effect was noted on cumulative exacerbations, asthma symptoms, or ACQ-5. Predefined subgroup analysis showed greater improvement in FEV_1 in patients with a BEC >300 cells/mL (LSM: lenzilumab 253 mL [95% CI 38 to 414] vs placebo 26 mL; p = 0.02).	Most frequent AEs in treatment group: rhinosinusitis and headache. No evidence of PAP-like effects.

(*Continued*)

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Table 3 (Continued).

Target	Biologic	Phenotype/ Pathway Targeted	Indication	Trial Type	Registration #	Population	Primary Results	Secondary Results	Safety
IL-2Ra (CD25)[126]	Daclizumab	Adaptive immunity, T cells	Moderate-to-severe chronic asthma	Ph2	NCT00028288	n=115	In moderate-to- severe chronic asthma, daclizumab improved FEV_1 (p=0.05), and reduced daytime asthma symptoms (p=0.018) and SABA use (p=0.009). Daclizumab treatment prolonged time to exacerbation (p=0.024). Increased SAE in treatment vs PBO.	Other findings included reduced daytime asthma symptoms as recorded in the daily diary (daclizumab - 1.2 ± 0.4 vs placebo 0.1 ± 0.4; p = 0.018) at 12 weeks. There was no difference in the time to severe exacerbation (defined as SCS use) during the active treatment phase (20 weeks), but a statistically significant difference became apparent by the end of study (36 weeks; p = 0.02). Mean BEC decreased 26% from baseline at week 12 in the treatment arm (vs 9% increase in placebo).	During study, AE was similar, but 3 drug subjects had SAE related to drug (anaphylactoid reaction requiring intubation), varicella zoster herpes viral meningitis, and diagnosis of breast cancer 4 months after last infusion. No further asthma studies pursued but approved for multiple sclerosis in 2016. Voluntarily withdrawn worldwide by manufacturers because of 8 cases of inflammatory encephalitis and meningoencephalitis (3/ 02/2018).[127]
IL-17a[128]	Secukinumab (AIN457)	Th17 immunity	Moderate-severe persistent asthma	Ph2	NCT01478360	n=46	No improvements in ACQ (10 mg/kg IV): LSM (90% CI); secukinumab −0.173 (−0.425 to 0.079) vs placebo −0.007 (−0.380 to 0.365).		

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IL-17Ra[129]	Brodalumab	Th17 immunity	Moderate-severe persistent asthma	Ph2	NCT01199289	n=302	No clinically significant difference was observed between the groups in terms of ACQ score from baseline to Week 12	Key secondary endpoints included change in pre- and post-bronchodilator FEV_1, rescue SABA use, daily asthma symptom score, and symptom-free days. No clinically meaningful differences in FEV_1 or symptoms scores were seen. Across nine prespecified subgroups for analysis (including stratification by high or low BEC [≥6% vs <6%]), only stratifying by bronchodilator reversibility (</≥ 20% reversibility) demonstrated a differential clinical response to brodalumab. Specifically, in the high-reversibility group, ACQ-7 scores at week 12 trended toward improvement in the brodalumab groups (max effect seen with the 210-mg dose, −0.820 vs placebo −0.287), an effect not seen in the low-reversibility group.	
IL-23 (p19 subunit)[130]	Risankizumab	Th17 immunity	Moderate-severe persistent asthma	Ph2a	NCT02443298	n=214	Decreased time to asthma worsening compared to PBO		

(*Continued*)

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Table 3 (Continued).

Target	Biologic	Phenotype/ Pathway Targeted	Indication	Trial Type	Registration #	Population	Primary Results	Secondary Results	Safety
IL-6r[131]	Tocilizumab	IL-6 trans-signaling	Mild-to-moderate, stable, allergic asthma; rs2228145 +AC or CC risk allele	POC, Ph2	ACTRN12614000123640	n=11	No significant differences in the primary endpoint were observed between study arms: late asthmatic response, maximum percentage fall in FEV_1 and AUC of the percent fall in FEV_1. Registered at Australian New Zealand Clinical Trials Registry.		

Abbreviations: ACQ, Asthma Control Questionnaire; AE, adverse event; AQLQ, Asthma Quality of Life Questionnaire; AUC, area under the curve; BEC, blood eosinophil count; CI, confidence interval; ED, emergency department; ETN, entanercept; FeNO, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in one second; ICS/LABA, inhaled corticosteroid/long-acting β_2-agonist; LSM, least-square mean; MCCT, methacholine challenge testing; PAP, pulmonary alveolar proteinosis; PBO, placebo, PC20, provocative concentration resulting in 20% reduction in FEV_1; PEF, peak expiratory flow; Ph, Phase; POC, proof of concept; SABA, short-acting beta-agonists; SAE, serious adverse event; SCS, systemic corticosteroids; SD, standard deviation; TNF, tumor necrosis factor.

primary endpoint was change in percent predicted FEV_1 compared to baseline following 12 weeks of treatment. No significant differences were noted in any efficacy endpoints, although the drug was well-tolerated with no significant difference in the incidence of "any infections" across treatment arms. No other large TNF-α inhibitor studies have been published in the last 10 years.

Antitrophic Factor Biologics

Lenzilumab (KN003) is a human IgG1 monoclonal antibody (IV) that binds GM-CSF and blocks interaction with its receptor. Lenzilumab has been studied in chronic myelomonocytic leukemia, COVID-19 pneumonia, and asthma, but is not currently approved for any indication.[138] GM-CSF canonically acts as a hematopoietic growth factor for granulocytes and macrophages, with a special role in alveolar macrophage differentiation and function. The heterodimer GM-CSF receptor is composed of a ligand-specific alpha-chain (CD116/CSF2RA) and the common beta-chain (CD131/CSF2RB).[139] GM-CSF levels are increased in the induced sputum of asthma patients and concentrations correlate with sputum eosinophilia in patients with moderate-severe asthma.[140] Given the proposed importance of airway granulocyte cytology (eosinophil vs neutrophil) to asthma phenotyping, GM-CSF emerged as a reasonable target for asthma therapeutic development in the 2010s in parallel with anti-IL5 antibodies.

Lenzilumab was studied in a phase 2, randomized, double-blind, placebo-controlled trial to evaluate the safety and efficacy of anti-GM-CSF therapy in a cohort of moderate-severe asthma patients inadequately treated with ICS and LABA cotherapy.[125] The primary endpoint was the change in FEV_1 compared to baseline at week 24 of therapy. The primary endpoint was not met, with a mean FEV_1 improvement of 118 mL in the treatment arm and 54 mL in the placebo arm (least-square mean, $p = 0.2$). The drug was generally well-tolerated but had an excess of mild-moderate infusion reactions in the active arm vs placebo arm. Given the association of autoimmune anti-GM-CSF antibodies with pulmonary alveolar proteinosis, patients' serum levels of surfactant protein were also monitored during the trial and no differences between treatment arms were noted.[141] No other asthma trials using an anti-GM-CSF drug have been published to date.

Adaptive Immune Modulators

Anti-Activated T-Cell Biologic

Daclizumab, a humanized monoclonal antibody targeting the high-affinity IL-2RA; also CD25), was first developed as a rejection prophylaxis agent for kidney transplant recipients (approved 1997) and subsequently developed for relapsing forms of multiple sclerosis (approved 2016).[142,143] IL-2 is a trophic cytokine largely expressed by activated T cells; it drives cell proliferation and survival of naïve, effector, and regulatory T cells, and has a range of effects on other lymphoid and nonlymphoid immune cells.[144] Blockade of CD25 by daclizumab greatly diminishes IL-2 signaling, leads to moderate reduction in T-cell numbers, and drives expansion of NK cells.[144]

Daclizumab was studied in a phase 2, randomized, double-blind, placebo-controlled study in a cohort of patients with uncontrolled moderate-severe persistent asthma despite medium-high–dose ICS use.[126] At baseline, treatment arms showed very similar biomarkers, with approximately 2/3 of patients atopic (by specific IgE testing; daclizumab 65%, placebo 61.5%), and mean BEC was also equivalent (0.2 ± 0.02 k/m^3 for both arms). Daclizumab showed a significant difference in its primary endpoint (change in $\%FEV_1$ compared to baseline at 12 weeks; daclizumab $4.4\% \pm 1.8\%$ vs placebo $1.5\% \pm 2.39\%$; $p = 0.05$),[126] although in absolute terms this was only a mean 60-mL improvement in FEV_1 (minimal clinically important difference = 100 mL)[145] for the daclizumab arm (vs −5 mL change for placebo). While overall adverse event rates were comparable across treatment arms, the daclizumab arm showed a numerically higher rate of serious adverse events; 5 vs 1 in placebo), three of which were linked to study drug, including a case of varicella zoster viral meningitis. Unfortunately, the asthma trial serious adverse event meningitis case was likely prophetic, as daclizumab was voluntarily withdrawn from the market in 2018 after postmarketing reports of 12 cases of serious inflammatory brain disorders, including encephalitis and meningoencephalitis.[146] The observed clinical benefit of daclizumab in asthma was likely through a nonselective anti-T-cell effect, blocking Th2 cells and reducing production of T2 cytokines, but at the expense of broad T-cell immune suppression. No other asthma trials using an anti-CD25 drug have been published to date.

Anti-Th17 Biologics

In recent years, interest in the IL-17 family and pulmonary disease has increased.[147] The six characterized IL-17 family members (IL-17A to IL-17F) are primarily homodimers (with the exception of heterodimer IL-17AF) and bind an array of dimeric receptor complexes (IL-17RA to IL-17RE).[147] IL-17a (also referred to as IL-17/CTLA-8) is the prototypical family member and is primarily expressed by the Th17 T-cell subset and to a lesser extent by γδT cells, NK cells, neutrophils, and other immune cells. IL-17A, IL-17F, and IL-17E are all reported to be elevated in the airways of severe asthmatics.[148,149] IL-17RA is the most widely expressed receptor monomer and it forms dimers with all of the other more tissue-restricted IL-17R proteins.[150] IL-17RA-RC is the most promiscuous IL-17R complex, binding IL-17A, IL-17F, and IL-17AF. IL-17RA-RB binds IL-17E (IL-25) and can drive Th2 immune responses.[149,151]

Secukinumab (AIN457), initially approved in 2015, is a human IgG1 monoclonal antibody that binds IL-17A (and IL-17AF with lower affinity) and inhibits their interaction with receptors IL-17RA-RC and IL-17RA-RD.[152–154] The drug is indicated for treatment of plaque psoriasis, psoriatic arthritis, ankylosing spondylitis, and hidradenitis suppurativa, as well as other rheumatologic conditions.[152] Secukinumab was studied in a phase 2, randomized, double-blind, placebo-controlled study in adults with uncontrolled moderate-severe persistent asthma despite medium-high–dose ICS/LABA and BECs <400 cells/mL at baseline.[128] The primary endpoint was improvement in asthma symptoms, as measured by Asthma Control Questionnaire (ACQ)-6 at 12 weeks compared to baseline, and no significant improvement was observed (least-square mean [90% confidence interval (CI)]; secukinumab −0.173 [−0.425 to 0.079] vs placebo −0.007 [−0.380 to 0.365]).[128] To our knowledge, this is the only clinical data evaluating secukinumab in asthma.

Brodalumab (AMG 827), approved in 2017, is a human IgG2 monoclonal antibody that binds IL-17RA and inhibits the biologic activity of 5 of the 6 known IL-17 family ligands (all except IL-17D).[150,155,156] It is approved for treatment of moderate-severe plaque psoriasis in adults who have failed to respond or have lost response to other systemic therapies.[155] Brodalumab was studied in a dose-ranging, phase 2a, randomized, double-blind, placebo-controlled study for adults with uncontrolled moderate-severe persistent asthma despite medium-high–dose ICS.[129] During the study, only ICS asthma controller medications were allowed and all others, including LABAs, were discontinued. Subjects in each treatment arm had similar levels of BECs (median 2.9% in both treatment groups) and total serum IgE (brodalumab 122 IU/mL vs placebo 144 IU/mL). The primary endpoint was change from baseline in ACQ-7 at 12 weeks. For the overall population, no significant change was seen in ACQ-7 scores (at any time point). A second phase 2 study was terminated early following an interim analysis that showed lack of efficacy.[157]

Risankizumab, initially approved in 2019, is a humanized IgG1 monoclonal antibody that binds the p19 subunit of the IL-23 dimer and blocks its interaction with the IL-23 receptor. This biologic is currently indicated for moderate-severe plaque psoriasis, psoriatic arthritis, and moderate-severely active Crohn's disease.[158] Risankizumab was studied in a phase 2a, randomized, double-blind, placebo-controlled study in adults with uncontrolled moderate-severe persistent asthma despite medium- or high-dose ICS and one additional controller plus a history of severe exacerbation in the last 12 months.[130] At baseline, the treatment arms showed similar median BECs (risankizumab 375 cells/mm^3 vs placebo 360 cells/mm^3), median sputum neutrophil fractions (risankizumab 60% vs placebo 54%), and median total serum IgE (risankizumab 398 mg/L vs placebo 485 mg/L). The primary endpoint was the time to first asthma worsening during 24 weeks of treatment (defined as meeting any of 4 criteria including reduced morning peak flow, increased rescue medication use, ACQ-5 score worsening, and exacerbation requiring systemic steroid use). Unfortunately, risankizumab not only failed to meet its primary endpoint, but appeared to worsen subjects' asthma, with a significant shortening of the time to first asthma worsening (risankizumab 40 days vs placebo 86 days; hazard ratio 1.46 [CI 1.05 to 2.04]; p = 0.03). Primary endpoint subgroup analysis indicated subjects with high BEC (≥200 cell/mL) fared worse with risankizumab (hazard ratio 1.76 [CI 1.15 to 2.7]) compared to subjects with lower BECs (<200 cells/mL; hazard ratio 1.1 [CI 0.65 to 1.86). At 24 weeks, risankizumab did not alter baseline sputum eosinophil or neutrophil cell counts, did not significantly reduce baseline sputum IL-6, and did not reduce baseline FeNO compared to controls.

Tocilizumab, initially approved in 2010, is a humanized IgG1 monoclonal antibody that binds both the soluble and membrane-bound IL-6 receptor, blocking IL-6 signaling via the classical and trans-signaling pathways.[159,160] IL-6 is a pro-inflammatory pleiotropic cytokine implicated in local (especially joint) inflammation and systemic inflammation,

driving acute-phase protein production and skewing T cells towards Th2 and Th17 differentiation.[160,161] Tocilizumab is currently indicated for rheumatoid arthritis, giant cell arteritis, systemic juvenile idiopathic arthritis, cytokine release syndrome, and various other inflammatory conditions.[162] Multiple studies have implicated IL-6 in asthma pathology, especially obesity- and metabolic dysfunction-associated asthma.[163] Other studies have shown elevated levels of serum IL-6[164] and airway IL-6 in patients with asthma.[161] Tocilizumab was studied in asthma in a small phase 2, proof-of-concept study enrolling stable mild allergic asthmatics with a genetic marker (rs2228145) predicting enhanced IL-6 trans-signaling.[131] The randomized, double-blind, placebo-controlled study focused on allergen inhalation challenges, which were performed before and after treatment with a single IV dose of tocilizumab or placebo. Subjects were weaned off asthma medications (including ICS for a minimum of 4 weeks) before initiation of the trial. The primary endpoint was the late asthmatic response assessed 3–7 hours after allergen challenge, both at baseline and 7 days after the experimental treatment. The late asthmatic response outcome was quantified as the maximal % fall in FEV_1 and area under the curve of the % fall in FEV_1. Unfortunately, the trial was stopped following an interim futility analysis that noted no effect in the primary and other secondary endpoints. Biomarkers showed no change in sputum eosinophil and neutrophil fractions, while serum C-reactive protein did transiently drop following treatment with tocilizumab.

Conclusion

Advanced biologic therapies for asthma have emerged following the identification of key predictive biomarkers (BEC, FeNO, specific IgEs to perennial aeroallergens) linked to distinct asthma phenotypes. Tracing the inflammatory pathways upstream from the classic asthma biomarkers led to the discovery that the maladaptive inflammatory responses initiated by the bronchial epithelium drive many forms of asthma. Diverse airway triggers (infectious, allergic, irritant, osmotic) activate the bronchial immune response and contribute to asthma pathogenesis in susceptible individuals. Despite the ongoing debate that exists around the optimal target(s) for disrupting asthma-associated inflammation, the T2 immune pathways are the predominant driver of disease. While the mixed immune responses (T2, T17, T1, innate) associated with asthma emphasize the disease heterogeneity, only biologic therapies with some degree of anti-T2 activity have been successful to date. Ongoing research will continue to probe for non-T2 mediators that have a specific role in driving asthma symptoms in specific patients/populations.

Data Sharing Statement

Qualified researchers may request data from Amgen clinical studies. Complete details are available at the following: https://wwwext.amgen.com/science/clinical-trials/clinical-data-transparency-practices/.

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Disclosure

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