



Asthma and the Biologics Revolution, Part 2: Failures and the Future Potential

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Abstract

Purpose of this review To highlight the evidence behind the various biologics that are being developed for asthma along with their specific targets in the inflammatory cascade and the potential role they serve in the management of allergic asthma.

Recent findings The mainstay of asthma management for the majority of asthmatics is inhaled corticosteroids with or without long-acting beta-agonists and/or leukotriene modifiers and/or tiotropium. However, in the small group of individuals with severe asthma uncontrolled with conventional therapy, biologics have emerged as an effective therapeutic option.

Summary Asthma is a chronic heterogeneous disease affecting both children and adults. In its severe form, asthma is associated with significant morbidity and mortality along with increased healthcare utilization and costs. Several biologics targeting different areas of the asthmatic inflammatory cascade such as IgE and IL-5 have been approved for the management of severe allergic asthma. Recent advances have helped to further uncover the pathophysiology of asthma which have identified other potential targets for therapy in the moderate-to-severe difficult to treat asthmatic population.

Introduction

Asthma is a chronic inflammatory respiratory disease affecting all ages and is defined by variable airflow limitation causing airway hyperresponsiveness and reversible airway obstruction [1, 2]. There is growing understanding that asthma is a complex heterogeneous disease with various phenotypes that extends beyond this simplified definition [2]. Phenotypically, asthma is commonly divided into allergic and non-allergic asthma with fluctuating disease severity that includes the full range of mild to severe. The majority of severe asthmatics have been found to have allergic asthma with elevated IgE, eosinophils, and several cytokines involved in the type 2 inflammation that contributes to its pathogenesis [3–7]. The mainstay treatment of asthma has been inhaled corticosteroids (ICS), and in those with more severe asthma, the addition of long-acting beta2-agonists (LABA), leukotriene modifiers, and tiotropium has been found to be beneficial. ICS help to minimize morbidity and mortality through reducing inflammation and improving lung function, decreasing severity and frequency of asthma exacerbations along with

hospitalizations, and improving quality of life [2]. However, not all asthmatics are responsive to high-dose ICS or systemic glucocorticoid treatments [8]. These refractory severe asthmatics not only have increased healthcare utilization and costs, but are also limited in therapeutic options to manage their disease [9]. Furthermore, the negative side effects with long-term use of inhaled and systemic glucocorticoids that include but are not limited to adrenal suppression, osteoporosis, stunted growth, diabetes, dysphonia, cataracts, glaucoma, thinning of the skin with easy bruising, and candidiasis have pushed for uncovering other treatment options [2]. The recent approval of anti-IgE and anti-IL5 biologics for severe asthma has provided new hope in treating this challenging population. This article aims to review the clinical efficacy of several novel therapeutics targeting different facets of the inflammatory cascade of allergic asthma that are being currently developed and those that have failed to demonstrate benefit despite initially showing promise.

Anti-IgE

IgE has been found to be instrumental in contributing to the early- and late-phase inflammatory response of asthma [10]. There is a high prevalence of allergen sensitization through a positive skin test among asthmatic patients [11]. Once B lymphocyte cells mature into plasma cells, they release IgE, which binds to the FcεRI on mast cells, basophils, eosinophils, and dendritic cells [10]. This results in receptor aggregation and cell activation and thereafter mast cell degranulation leading to a cascade of mediators that include histamine, tryptase, chymase, heparin, lipid-derived eicosanoids, leukotrienes, cytokines, chemokines, growth factors, and prostaglandins to be released, which subsequently leads to the bronchoconstriction effects of asthma [10, 12]. Hence, IgE became an attractive target as a means of asthma therapy and resulted in the first biologic, omalizumab (Xolair), being developed in the late 1990s [13]. Omalizumab, currently the only approved anti-IgE for asthma, is reviewed in detail in the article entitled “Asthma and the Biologics Revolution Part 1: Here and Now”. To overcome limitations of omalizumab, other more potent forms of anti-IgE were sought.

Ligelizumab (QGE031B) is a humanized monoclonal antibody that has almost 50-fold higher affinity for the IgE receptor FcεRI than omalizumab in vitro which translates to a 6- to 9-fold greater potency in vivo. The first clinical trial with ligelizumab administered a single dose of ligelizumab (0.1–10 mg/kg) or placebo intravenously, whereas the second clinical trial

administered two to four doses of ligelizumab (0.2–4 mg/kg) or placebo subcutaneously at 2-week intervals. Results from the 2 phase I randomized, double-blind, placebo-controlled clinical trials have shown that ligelizumab inhibits allergen-induced skin test responses and reduce IgE levels to a greater and longer extent than omalizumab in atopic patients [14, 15]. However, further clinical trials of ligelizumab were discontinued after it failed to meet the primary objective of demonstrating superiority versus placebo in asthmatic patients ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT02075008) Identifier: NCT02075008).

Great interest has also come from targeting IgE-expressing B cells before they differentiate into IgE-secreting plasma cells and consequently allowing for a reduction in the amount of circulating IgE [16, 17]. Quilizumab (RG7449) is a humanized monoclonal antibody that binds to the M1 prime segment of membrane IgE and targets B lymphocytes before they produce IgE as oppose to neutralizing existing free IgE. It has been shown to inhibit both the early and late asthmatic responses by approximately 30% and reduce serum IgE levels by approximately 40% [18]. However, clinical trials of quilizumab in patients with severe asthma did not show any therapeutic benefit and ongoing development of the drug was ceased [19].

The low affinity Fc ϵ RII (CD23) on B cells that regulates IgE production served as another potential target. Lumiliximab, a humanized anti-CD23 IgG1 monoclonal antibody that cross-links CD23 on B cells, decreased serum IgE levels but did not show any clinical benefit in asthmatic patients [20].

Anti-Interleukins

Interleukins have been demonstrated to be a major role in the inflammatory cascade of asthma and thus have been the focus of targeted asthma therapy [21].

IL-1

Interleukin 1 (IL-1) is a cytokine that has pro-inflammatory effects. Two types of IL-1 exist, alpha (α) and beta (β), that differ in molecular structure but have a similar function in that they act on the same receptor, the IL-1 receptor-a. IL-1Ra acts as a regulator of IL-1 signalling as it is a natural inhibitor of IL-1 [21]. IL-1 β levels have been found to be increased in bronchoalveolar lavage (BAL) fluid of patients with symptomatic asthma [22]. Anakinra, a recombinant form of human IL-1 receptor antagonist (IL-1Ra), is currently being assessed in clinical trials as a rescue treatment for allergic airway inflammation ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study?term=NCT03513458) Identifier: NCT03513458).

IL-2

Increased CD 25+ T cells, levels of IL-2, and soluble IL-2 receptor (CD25) have found to be involved in the airway inflammation of patients with severe asthma [23, 24]. Daclizumab is a humanized IgG1 monoclonal antibody against the IL-2 receptor alpha-chain (IL2RA) of activated lymphocytes. A randomized, double-blind, placebo-controlled study looked at the efficacy and safety of daclizumab in patients with moderate-to-severe persistent asthma randomized patients to either receive daclizumab or placebo every 2 weeks for 12 weeks with an ICS tapering phase of 8 weeks while on the study drug. There were only small

significant improvements in FEV1, daytime asthma symptoms, increased time to exacerbation, and short-acting beta2-agonist in patients treated with daclizumab. Despite these findings, there were significant adverse events including anaphylactoid reactions and viral meningitis in the daclizumab-treated group [25]. Although daclizumab may play a role as an add-on therapy in the treatment of moderate-to-severe asthma, its utility may be limited as it is without meaningful risks.

IL 4 and IL 13

Interleukins 1 and 5 are not the only interleukins to play a role in the pathogenesis of eosinophilic asthma. Interleukin 4 (IL-4) induces uncommitted Th0 cell differentiation into Th2 cells and its expansion, causes isotype switching of B cells to increase IgE synthesis and upregulates the IgE receptors, increases eosinophil recruitment to the lungs, and upregulates expression of vascular cell adhesion molecule 1. IL-4 also effects airway remodelling by upregulating collagen and fibronectin production [7, 26]. Initial allergen-induced asthma murine studies of IL-4 or its receptor antagonists demonstrated promising results as there was reduction of eosinophils into the airways, IL-5 release from T cells, serum IgE, lung inflammation, and airway hyperresponsiveness to methacholine [27, 28]. However, these findings have not consistently been reproduced in humans.

Pascolizumab is a humanized monoclonal antibody that targets IL-4 and prevents it from binding its receptor. Monthly intravenous doses of up to 100 mg/kg were well tolerated in animal studies using cynomolgus monkeys and effective in neutralizing the bioactivity of IL-4 [29]. Despite this finding, a phase I/II randomized double-blind, placebo-controlled, parallel-group pilot study of pascolizumab in patients with symptomatic steroid-naïve asthma failed to show efficacy, and as a result, subsequent development of pascolizumab was halted ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00024544) identifier: NCT00024544).

Similar to pascolizumab, altrakincept, a soluble recombinant human IL-4R that contains the extracellular portion of the alpha-chain of the IL-4R but lacks the transmembrane and cytoplasmic domains needed to activate receptor-mediated intracellular signalling pathways and binds to IL-4, demonstrated encouraging results in murine models of asthma. Altrakincept inhibited eosinophil recruitment to the airways, late-phase lung inflammation, and hypersecretion [30]. These findings led to a phase I/II double-blind, placebo-controlled trial conducted by Borish et al. where 25 patients with moderate asthma requiring inhaled corticosteroids were randomly assigned to receive a single nebulized dose of altrakincept 1.5 mg, 0.5 mg, or placebo after stopping inhaled corticosteroids. Altrakincept was found to significantly improve FEV1 at both doses compared with placebo. The 1.5 mg dose of altrakincept was also shown to improve asthma symptom scores, significantly reduce beta2-agonist rescue use, and significantly reduce airway inflammation (demonstrated through decrease levels of FeNO) [31].

A further double-blind, placebo-controlled study by Borish et al. evaluating the clinical efficacy of altrakincept randomized 62 patients with moderately severe persistent asthma that were ICS-dependent to either receive 12 doses once weekly nebulisations of 0.75, 1.5, or 3.0 mg of altrakincept or placebo after discontinuation of their ICS. Altrakincept at a dose of 3 mg weekly was significantly better than

placebo in maintaining FEV1 after corticosteroid discontinuation, showed a trend to maintaining asthma symptom scores, and demonstrated ability to maintain function in the absence of adverse side effects [32]. Additional clinical trials could not demonstrate significant clinical benefit in terms of asthma symptoms and respiratory function (FEV1) ([ClinicalTrial.gov](https://clinicaltrials.gov/ct2/show/study/NCT00001909) identifier: NCT00001909). This resulted in the suspension of altrakincept production.

Much like IL-4, interleukin-13 (IL-13) is also a key component of eosinophil accumulation and migration, recruitment of basophils, and IgE production by B cells. Additionally, IL-13 contributes to the airway hypersensitivity response by directly impacting airway smooth muscle cell contractility, increases mucus production, and induces subepithelial fibrosis [7]. Furthermore, IL-13 has been demonstrated to be elevated in sputum and bronchial biopsies of patients with asthma that also had evidence of increased eosinophil levels [33, 34]. It is important to note that IL-13 acts on two receptors IL-4R α /IL-13R α 1 and IL-13R α 2, which then activates the transcription factor STAT6 [7]. The importance of IL-13 in the Th2 response in asthma pathogenesis led to the development of four monoclonal antibodies that inhibited IL-13 from binding to its receptors.

Lebrikizumab is a humanized IgG4 anti-IL13 monoclonal antibody and has been shown to be effective in reducing the IL-13-inducible gene encoding periostin [35]. When stimulated by IL-13, periostin, an extracellular matrix protein, is released by bronchial epithelial cells and causes airway remodelling in asthma [36]. Corren et al. through a randomized, double-blind, placebo-controlled study randomized 219 patients with moderate-to-severe asthma inadequately controlled despite being on ICS received either lebrikizumab 250 mg every month for 6 months or placebo. Before randomization, each patient's Th2 status (IL-13 signature surrogate) was characterized on the basis of a combination of the total serum IgE level and peripheral blood eosinophil count. Lebrikizumab was shown to improve lung function (FEV1) and indicate a trend of decreasing exacerbation rates. In fact, in the high Th2 group (defined as total IgE level > 100 IU/mL and an eosinophil count of ≥ 140 cells/ μ L) treated with lebrikizumab, there was a reduction of exacerbations by 60% when compared with placebo. There was no difference between the groups in regard to asthma symptom score and the use of rescue medications. Interestingly, subgroup analysis of patients treated with lebrikizumab, those with higher levels of serum periostin (in the upper 50th percentile), had greater improvement in lung function (FEV1) compared with their lower level counterparts. Similar predictive of response findings were noted with serum fraction of exhaled nitric oxide (FeNO) in that if the patient treated with lebrikizumab had higher pre-treatment levels, they had greater improvement in lung function. Levels of FeNO also were found to decrease with lebrikizumab treatment [35]. Noonan et al. investigated the efficacy and safety of IL-13 blockade with different doses of lebrikizumab in asthmatic patients not receiving ICS in a phase 2 study. Two hundred twelve patients were randomized to receive 125, 250, or 500 mg of lebrikizumab or placebo subcutaneously monthly for 12 weeks. There was no statically or clinically significant improvement in lung function (FEV1) between the dose groups and placebo group. This was also true in the subgroup analysis involving pre-treatment serum periostin levels. The authors concluded that although lebrikizumab may improve disease control, it would not be superior to the use of ICS in these patients [37]. These findings were also supported by a more recent phase 3 study [38].

Scheerens et al. took another approach and evaluated the efficacy and safety of lebrikizumab in subjects with mild allergic asthma that had evidence of house dust mite, cat dander, or ragweed sensitization in reducing the airway reaction to an inhaled aeroallergen solution via a bronchial allergen challenge. This phase 2 multicenter, double-blind clinical trial randomized 28 patients to receive either 1–5 mg/kg of lebrikizumab or placebo administered subcutaneously every 4 weeks over 12 weeks, for a total of four doses. Although not statistically significant, lebrikizumab was found to reduce the late asthmatic response (LAR) by 48% when compared with placebo. Exploratory analysis demonstrated that those treated with lebrikizumab with evidence of higher Th2 status in the form of elevated baseline levels of peripheral blood eosinophils, serum IgE, or periostin exhibited a greater reduction in LAR when compared with their lower Th2 counterparts. Lebrikizumab was also found to reduce the Th2 inflammation by decreasing serum IgE, chemokine ligands 13 and 17 [39].

LUTE and VERSE were replicate, double-blind, placebo-controlled studies evaluating multiple doses of lebrikizumab in patients with moderate-to-severe uncontrolled asthma despite the use of medium-to-high-dose ICS and a second controller. Two hundred fifty-eight (LUTE) and 205 (VERSE) patients were randomized to receive either lebrikizumab 37.5, 125, 250 mg or placebo subcutaneously every 4 weeks. Lower exacerbation rates were observed in the lebrikizumab treatment groups compared with placebo. The exacerbation rate reduction compared with placebo was more pronounced in periostin-high patients than in periostin-low patients. There was no clear dose-response for lebrikizumab on exacerbations [40]. Despite lebrikizumab's promising effects, the LAVOLTA I and LAVOLTA II phase 3 clinical trials of lebrikizumab that randomized patients with uncontrolled asthma to receive lebrikizumab 37.5 mg or 125 mg, or placebo subcutaneously, once every 4 weeks failed to consistently show significant reduction in asthma exacerbations in high Th2 biomarker patients (categorized as periostin ≥ 50 ng/mL or blood eosinophils ≥ 300 cells/ μ L) [41]. Subsequently, further evaluation of lebrikizumab was terminated in asthma.

Anrukinzumab (IMA 638) and IMA 026 are also humanized anti-IL-13 monoclonal antibodies. Anrukinzumab works by allowing interaction of IL-13 with IL-13 receptors, but prevents IL-4R α recruitment to the IL13/IL-13R α 1 complex, while IMA 026 directly competes with IL-13 in interacting with its receptors (IL13R α 1 and IL13R α 2). In two double-blind, placebo-controlled, parallel-group phase 2 trials, 55 patients with mild atopic asthma were randomized to receive two doses 1 week apart of either anrukinzumab 2 mg/kg subcutaneously, IMA 026 2 mg/kg subcutaneously, or placebo. Anrukinzumab reduced both the early- and late-phase asthmatic FEV1 response at day 14 but not day 35, whereas IMA 026 did not at either time points when compared with placebo. Furthermore, there were no significant changes in terms of blood or sputum eosinophil or total IgE with these drugs [42].

Two other anti-IL-13 monoclonal antibodies, dectrekumab (QAX576) and ABT-308, are currently being evaluated with regard to safety and efficacy via clinical trials in patients with moderate-to-severe persistent and mild-to-moderate controlled asthma ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01130064) identifier: NCT01130064 and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00986037) identifier: NCT00986037 respectively).

Although targeting IL-4 and IL-13 individually was unsatisfactory, the functional homogeneity between IL-4 and IL-13 continued to be of great interest with the development of therapies that targeted both

interleukins [7]. One of those was pitrakinra (Aerovant), a recombinant human IL-4 variant that competitively binds to the heterodimeric IL-4Ra-IL-13Ra1 receptor complex to interfere with the actions of both IL-4 and IL-13. In two independent randomized, double-blind, placebo-controlled, parallel group phase 2a clinical trials, 56 patients with mild-to-moderate atopic asthma were treated with pitrakinra or placebo via two routes. In study 1, patients were randomly assigned to receive either 25 mg pitrakinra or placebo by subcutaneous injection once daily. In study 2, patients were randomly assigned to receive either 60 mg pitrakinra or placebo by nebulisation twice daily. Inhaled allergen challenge was done before and after 4 weeks of treatment. Irrespective of route of administration, there was a decrease in FEV1 in response to allergen challenge that was attenuated after 4 weeks of treatment with pitrakinra, compared with placebo. Furthermore, inhaled pitrakinra was found to reduce the late asthmatic response and significantly reduced airway inflammation (measured by FeNO) compared with placebo [43]. In a phase 2b multicenter, placebo-controlled clinical trial of pitrakinra, whereby 534 participants with moderate-to-severe asthma inadequately controlled on the combination of ICS and LABA were randomized to receive either 1, 3, or 10 mg twice daily of inhaled pitrakinra or placebo over 12 weeks, there was no overall significant difference between pitrakinra therapy (irrespective of the dose) and placebo. However, statistically significant efficacy with a pitrakinra dose of 10 mg was observed in certain pre-specified subpopulations including eosinophilic asthma defined as a serum eosinophil level of > 350 cells/mm³ and upper tertile FeNO (range 20–122 ppb) [44]. Additionally, pharmacogenetic analysis indicated inhaled pitrakinra at this dose (10 mg) significantly reduced the number of asthma exacerbations in patients with a specific single nucleotide polymorphism (SNP) in the gene encoding IL-4R α located within the 3' untranslated and proximal region (rs8832GG and rs1029589GG genotypes respectively) [45]. Pitrakinra was generally well tolerated in all of these studies.

AMG 317 is a humanized monoclonal antibody that targets IL-4R α and both prevents the binding of IL-4 to its receptor and hinders IL-13 signalling activity. AMG 317 did not demonstrate clinical efficacy with no improvements in the control of asthma, beta2-agonist use, or lung function across the overall group of 294 patients with moderate-to-severe asthma on stable ICS in a phase 2, multicenter, randomized, double-blind, placebo-controlled study receiving weekly subcutaneous injections of placebo or AMG 317 (75, 150, or 300 mg) for 12 weeks. However, evidence of biologic effect with dose-responsive reduction in IgE and clinical activity was noted, especially in the AMG 317 300 mg dose group. All groups, including patients receiving placebo, demonstrated improvements in ACQ from baseline. Patients receiving the highest doses of AMG 317 experienced fewer exacerbations than patients receiving placebo or the lowest dose of AMG 317. Patients with higher baseline ACQ scores who received AMG 317 300 mg demonstrated a consistent trend of more clinically meaningful effects in change in ACQ, FEV1, and morning peak flow [46]. AMG 317 was fairly well tolerated in all these studies.

Tralokinumab (CAT 354) is an IgG4 humanized neutralizing IL-13 monoclonal antibody and was deemed safe with favourable pharmacokinetics in a

phase 1 multiple-dose, double-blind and placebo-controlled study, whereby 23 patients with mild asthma randomized to intravenous infusions of tralokinumab (1 mg/kg, 5 mg/kg, or 10 mg/kg) or placebo every 4 weeks [47]. Piper et al. further evaluated tralokinumab in a phase II double-placebo and placebo-controlled study where 194 patients with moderate-to-severe uncontrolled asthma despite being on controller therapies were randomized to receive either tralokinumab (150, 300, or 600 mg) or placebo subcutaneously every 2 weeks. When compared with placebo, tralokinumab did not affect ACQ. However, the authors noted evidence of treatment effect with tralokinumab as it did significantly improve lung function through increases in FEV1 from baseline, 8.1 (150 mg) to 16.1% (600 mg), and decreased the need for short-acting beta2-agonist rescue medication use. The authors point out the effect on FEV1 was observed in subjects with and without objective evidence of atopy, which was consistent in a previous study indicating that IL-13 mRNA is elevated in bronchial mucosa of both atopic and non-atopic subjects with asthma [48, 49]. When 56 of these patients that had a baseline sputum IL-13 level were stratified into sputum IL-13 positive or negative, there was an apparent association between the presence of IL-13 and response to tralokinumab as evident by changes in FEV1 [48]. In a phase 2b double-blind, placebo-controlled, parallel-group, multicentre study evaluating to assess the efficacy and safety of two dosing regimens of tralokinumab in patients with severe uncontrolled asthma as defined by using high ICS and a LABA with evidence of two to six exacerbations in the previous year. Four hundred fifty-two patients were randomized to receive either tralokinumab 300 mg or placebo either every 2 weeks to week 50, or every 2 weeks for 12 weeks followed by every 4 weeks to week 48. There was no improvement in annual asthma exacerbation rate between tralokinumab treatment groups and placebo. However, in a subgroup post hoc analysis, tralokinumab given every 2 weeks for 52 weeks demonstrated an improvement in FEV1, ACQ6, and asthma exacerbation rates in patients with higher biomarkers suggestive of IL-13 activation. This includes higher baseline serum periostin or DPP-4 levels than the population baseline median [50].

The MESOS phase 2 multicenter, double-blind, placebo-controlled trial found that tralokinumab does not substantially affect airway inflammation or remodelling in patients with moderate-to-severe asthma on a stable dose of ICS. Two hundred twenty-four patients were randomized to either receive tralokinumab 300 mg or placebo subcutaneously every 2 weeks. When compared with placebo, tralokinumab did not significantly affect bronchial, serum, or sputum eosinophil counts, but did significantly reduce FeNO and IgE concentrations. This hints that IL-13 may not be essential for eosinophilic airway inflammation control in moderate-to-severe asthma [51].

When evaluated in two large pivotal double-blind, placebo-controlled, phase 3 clinical trials in patients with severe asthma that were inadequately controlled despite use of ICS and LABA with the clinical characteristics identified by the phase 2b results, and to ascertain whether there was a subgroup, identified by a biomarker, with an enhanced response to tralokinumab therapy, tralokinumab had inconsistent findings. In the STRATOS I, 1207 participants were randomized to receive either tralokinumab 300 mg every 2 weeks, tralokinumab 300 mg every 4 weeks, or placebo subcutaneously. Whereas in STRATOS 2, participants were randomized to receive tralokinumab 300 mg or matching placebo subcutaneously every 2 weeks for 52 weeks. In both of these

phase 3 trials, tralokinumab 300 mg every 2 weeks (or every 4 weeks) did not significantly reduce the annual asthma exacerbation rate (AAER) when compared with placebo in the entire population. The biomarker analyses in STRATOS 1 identified FeNO as the preferred biomarker for predicting enhanced response to tralokinumab as the anti-IL13 monoclonal antibody every 2 weeks reduced AAER by 44% in FeNO-high (≥ 37 ppb) participants. In STRATOS 2, the enhanced effect on AAER reduction compared with the all-comers results was neither significant nor clinically meaningful, including in the FeNO-high group. DPP-4 and periostin did not consistently predict response to tralokinumab therapy, despite being identified as promising biomarkers of increased interleukin-13 activity in the phase 2b trial [52]. A 40-week double-blind trial evaluated the OCS-sparing potential of tralokinumab in patients with severe, uncontrolled asthma requiring maintenance OCS treatment plus ICS/LABA. One hundred forty patients were randomized to tralokinumab 300 mg or placebo administered subcutaneously every 2 weeks. Tralokinumab failed to demonstrate any OCS-sparing potential when compared with placebo [53]. Development of tralokinumab for asthma has since ceased. Tralokinumab was well tolerated in all studies.

IL 9

IL-9 is a pleiotropic cytokine also implicated in asthma pathogenesis as it stimulates mast cell growth and proliferation, increases IgE production by B cells, and upregulates the Fc ϵ RI. Given IL-9 overexpression correlates with smooth muscle cell hyperplasia, eosinophilic airway inflammation, mucus production, and airway hypersensitivity, it was targeted in the development of asthma therapies [7, 54].

MEDI-528 is a humanized IgG1 anti-IL9 monoclonal antibody and was deemed safe with favourable linear pharmacokinetics in a phase I dose-escalation study where single doses of MEDI-528 (0.3, 1.0, 3.0, or 9.0 mg/kg) were administered as an intravenous infusion (20 mg/min administered over 1–40 min, depending on dose) and by subcutaneous injection in healthy subjects [55]. This led to two randomized placebo-controlled phase 2a studies assessing the safety profile and potential efficacy of multiple subcutaneous doses of MEDI-528 in asthmatics. In the first study, 36 participants with mild asthma received MEDI-528 (0.3, 1, 3 mg/kg) or placebo subcutaneously twice weekly for 4 weeks, whereas in the second study, 7 participants with mild-to-moderate asthma and exercise-induced bronchoconstriction received 50 mg MEDI-528 or placebo subcutaneously twice weekly for 4 weeks. Overall, asthma symptom scores showed a trend toward improvement in all subjects. A trend toward fewer subjects having ≥ 1 asthma exacerbation was observed in MEDI-528-treated subjects in study 1 compared with placebo. In study 2, a protective effect against exercise-induced bronchoconstriction was observed with 50 mg of MEDI-528 compared with placebo. The authors noted that caution should be taken in interpreting these findings given the small sample size [56]. Oh et al. conducted a phase 2b double-blind, multicenter, parallel-group clinical trial to evaluate the efficacy and safety of subcutaneous MEDI-528 in 329 subjects with uncontrolled moderate-to-severe asthma on or eligible for medium to high doses of ICS. Participants were randomized to either receive subcutaneous MEDI-528 (30, 100, or 300 mg) or placebo every 2 weeks for 24

weeks along with their usual asthma medications. Unfortunately, MEDI-528, irrespective of dose, failed to improve ACQ-6 scores, asthma exacerbation rates, or FEV1 values, and thus, its development for asthma was discontinued [57], although MEDI-528 was well tolerated with no major side effects.

IL 17 and IL 23

IL-17A and IL-17F are pro-inflammatory cytokines that are released by Th17 cells and have also been implicated in asthma pathogenesis. The overexpression of these interleukins promotes the recruitment of both neutrophils and eosinophils into the airways and has been found to be present in the bronchial biopsies of patients with severe asthma [7].

Secukinumab (AIN457) is an IgG kappa IL-17A-specific humanized monoclonal antibody that was developed as a hopeful new asthma therapy. However, phase II clinical trials in moderate-to-severe asthmatic patients not adequately controlled with ICS and LABA patients have been terminated and there are no plans to further investigate this drug in asthma ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01478360) Identifier: NCT01478360). Instead of targeting only IL-17, blocking its receptor to inhibit the IL-17 signalling cascade was also proposed and developed in the form of brodalumab (AMG827), an IgG2 IL-17RA-specific humanized monoclonal antibody. Its safety and efficacy was evaluated in a phase 2 trial in patients with moderate-to-severe asthma that was not adequately controlled with ICS and LABA. The hundred two patients were randomized to receive either brodalumab (140, 210, or 280 mg) or placebo subcutaneously every 2 weeks for 10 weeks. Disappointingly, brodalumab did not show any clinical benefit when compared with placebo [58]. It remains to be determined if brodalumab development for asthma is continued as some patients committed suicide in clinical trials evaluating brodalumab for plaque psoriasis, although no causal relationship between suicidal thoughts and behaviour have been established with brodalumab [59].

IL-23, a growth factor and inducer of Th17 cells, poses as another target of interest as its blockade in murine studies resulted in decreasing recruitment of neutrophils, eosinophils, and lymphocytes into the airways [60]. Risankizumab (Skyrizi) is a humanized monoclonal antibody targeting IL-23A and is currently undergoing phase II clinical trials in asthma ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT02443298) Identifier: NCT02443298).

IL25, IL33, and TSLP

IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) produced in airway epithelial cells stimulate the Th2-mediated inflammatory response in asthmatics and serve as potential targets of novel asthma therapies. More specifically, IL-25, also known as IL-17E, was found to cause eosinophilia through the production of IL-5 and other Th2 cytokines that include IL-4, IL-13, and eotaxin [7]. In fact, increased IL-25 levels in plasma and the expression of IL-17RA and IL-17RB was found higher on eosinophils in allergic asthma patients compared with non-asthmatic controls [61]. IL-25 has also been increased in expression in asthmatic bronchial mucosa and dermis of sensitized atopic subjects after allergen provocation [62]. Both IL-25 and IL-33 have been shown to be fundamental for induction of Th2-type cytokine-mediated allergic airway eosinophilia in murine studies [63]. TSLP has been found to be increased in the airways of patients with asthma with its level of elevation correlating with disease severity [64, 65].

Etokimab (ANB 020) and RG 6149 (AMG 282) are humanized monoclonal antibodies that inhibit IL-33 and the binding of IL-33 to its receptor (ST2) respectively. They are currently being evaluated as potential therapies for patients with asthma in clinical trials ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03469934) Identifier: NCT03469934 and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT01928368) Identifier: NCT01928368 respectively).

Tezepelumab (AMG 157) is an IgG2 λ humanized monoclonal antibody that prevents the interaction of TSLP with its receptor complex. In a phase 1 double-blind, placebo-controlled study, 31 patients with mild allergic asthma were randomized to receive three monthly doses of tezepelumab (700 mg) or placebo intravenously. Tezepelumab was found to attenuate most measures of allergen-induced bronchoconstriction in early and late asthmatic responses when compared with placebo. In addition, patients receiving tezepelumab had significant decreases in markers of systemic and airway inflammation in the form of levels of blood and sputum eosinophils, and FeNO before and after the allergen challenge [66]. In a phase 2 double-blind, placebo-controlled trial, 584 patients with uncontrolled moderate-to-severe asthma on medium to high ICS and a LABA were randomized to receive either tezepelumab 70 mg every 4 weeks (low dose), 120 mg every 4 weeks (medium dose), 280 mg every 2 weeks (high dose), or the equivalent placebo over a 52-week period. Tezepelumab was found to significantly lower rates of annual asthma exacerbations (61%, 71%, and 66% respectively) when compared with placebo. Interestingly, these findings were independent of baseline blood eosinophil counts, FeNO levels, or Th2 status (determined via IgE and blood eosinophil levels). However, similar to the phase I study, tezepelumab was found to reduce blood eosinophil counts, FeNO levels, and total serum IgE levels [67•]. Tezepelumab also demonstrated better asthma control in this population through clinically meaningful improvement in ACQ-6 in all regimens when compared with placebo [68]. These promising findings have expedited tezepelumab evaluation in phase 3 clinical trials and whether it has an OCS-sparing effect in patients with OCS-dependent asthma ([ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03347279) Identifier: NCT03347279 and [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT03406078) Identifier: NCT03406078).

Anti-Prostaglandins

The prostaglandin D2 (DP2) receptor pathway possesses an interesting potential novel target for allergic asthmatics. Prostaglandin D2 (PGD2) is a predominant cyclooxygenase metabolite of arachidonic acid and is released by mast cells and T helper cell (Th) type 2 lymphocytes [69, 70]. PGD2 is a potent bronchoconstrictor and has been found to be increased in allergic asthmatics after allergen provocation to house dust mite *D. pteromyssinus* [69]. These findings suggest that PGD2 is involved in the asthmatic inflammatory response. PGD2 is an agonist of two seven-transmembrane G-protein-coupled receptors known as prostaglandin DP receptors 1 and 2. DP2, also known as a chemoattractant receptor expressed on Th2 cells (CRTH2), is primarily found on Th2 cells, eosinophils, and basophils, and is involved in their recruitment, activation, and migration to the airways. When bound to PGD2, there is a release of type 2 cytokines IL-4, IL-5, and IL-13 leading to the allergic inflammatory cascade [71, 72].

Timapiprant (OC000459), fevipiprant, and setipiprant (ACT-129968) are potent, orally administered, CRTH2 antagonists that have been investigated for use in asthma. In mildly allergic asthmatic patients, oral timapiprant at a dose of 200 mg BID was found to decrease the post-allergen increase in sputum eosinophil and the late asthmatic response (LAR), but not EAR when compared with placebo in a randomized, double-blind, placebo-controlled, two-way crossover proof of concept study [73]. In a phase 2 double-blind, parallel group trial in 132 steroid-free patients with moderate persistent asthma randomized to receive oral timapiprant 200 mg BID or placebo for 4 weeks, the timapiprant-treated group had a trend toward a greater improvement in lung function (significant in per protocol analysis) and significant improvement in AQLQ when compared with placebo. Furthermore, when OC000459 treatment was stopped, there was a decline in FEV1 toward the baseline value [74].

To determine which subpopulation of asthmatic patients that would be most responsive to timapiprant in a dose defining double-blind parallel group study, Pettipher et al. randomized 519 patients with moderate persistent asthma to receive at oral timapiprant at three dose levels (25 mg once daily, 200 mg once daily, or 100 mg twice daily) or placebo for 12 weeks and found that timapiprant, irrespective of dose, improved lung function (FEV1) and ACQ and AQLQ scores when compared with placebo. Subgroup analysis indicated that atopic subjects with active disease ($ACQ \geq 1.5$) and blood eosinophil counts ≥ 250 cells/ μ L, but not < 250 cells/ μ L had the most improvement in lung function and ACQ and AQLQ scores, with eosinophilia having a heightened effect when compared with placebo. Intriguingly, younger patients (≤ 50 years old) had a greater response with timapiprant, which the authors indicate may reflect greater Th2 dominance in younger patients [75].

The initial phase II clinical trial of fevipiprant (QAW039) was not reassuring as the exploratory double-blind, randomized, placebo-controlled multicenter study demonstrated no difference in lung function or symptom scores when mild-to-moderate uncontrolled allergic asthma with a positive skin prick test to local allergens was treated with fevipiprant at a dose of 500 mg PO daily when compared with placebo. However, a subgroup analysis revealed that patients with greater severity of airflow limitation ($FEV1 < 70\%$) had improved lung function and asthma control when treated with fevipiprant [76]. In moderate-to-severe eosinophilic asthmatics as evident by an elevated sputum eosinophil count ($\geq 2\%$), fevipiprant 225 mg PO BID decreased sputum eosinophil counts, improved AQLQ scores and ACQ-7 scores in the predefined subgroup of patients who had uncontrolled asthma at baseline, and improved post-bronchodilator lung function (FEV1) compared with placebo, although fevipiprant did not have any significant effect on blood eosinophil count [77]. In a phase 2b clinical trial, 1058 patients with allergic asthma uncontrolled by low-dose ICS were randomized to 12 weeks' treatment with PO once-daily (1, 3, 10, 30, 50, 75, 150, 300, or 450 mg) or twice-daily (2, 25, 75, or 150 mg) fevipiprant and montelukast 10 mg once daily or placebo; fevipiprant significantly

improved lung function (FEV1) when compared with placebo. This finding was also evident in the montelukast-treated group when compared with placebo. Unfortunately, the study was not powered for a comparison between fevipirant and montelukast in regard to this endpoint. There was no effect observed with fevipirant on FeNO levels, asthma symptom control, quality of life, or work productivity and daily activities. Furthermore, there was no evidence of higher efficacy in terms of FEV1 based on blood eosinophil levels [78•]. Currently, fevipirant continues to be evaluated in clinical trials for asthma ([ClinicalTrials.gov Identifier: NCT03226392](https://clinicaltrials.gov/ct2/show/study/NCT03226392), [ClinicalTrials.gov Identifier: NCT03052517](https://clinicaltrials.gov/ct2/show/study/NCT03052517)). GB001 (ADC-3680), another CRTH2 antagonist, has shown to decrease airway inflammation through reducing FeNO levels in mild atopic asthmatics on ICS. It along with MK-1029, another CRTH2 antagonist, is being assessed in clinical trials for asthma ([79] [ClinicalTrials.gov Identifier: NCT03683576](https://clinicaltrials.gov/ct2/show/study/NCT03683576), [ClinicalTrials.gov Identifier: NCT01730027](https://clinicaltrials.gov/ct2/show/study/NCT01730027), [ClinicalTrials.gov Identifier: NCT01370317](https://clinicaltrials.gov/ct2/show/study/NCT01370317)).

On the other hand, when evaluated in a phase 2a double-blinded, placebo-controlled, cross-over study in 18 mild asthmatic males, setipirant at a dose of 1000 mg BID for 5 days significantly reduced the allergen-induced LAR, but not the EAR and airway hyperresponsiveness (AHR) when compared with placebo [80]. Additional evaluation of setipirant, along with other CRTH2 antagonists such as AZD-1981, QAV-680, AZD-5985, AZD-8075, MK-7246, and RG-7185 for asthma, has ceased [81, 82]. Further clinical trials are needed to evaluate the efficacy and safety of this class of drugs to determine their role in the management of asthma.

Anti-TNF- α

TNF- α is a pleiotropic pro-inflammatory cytokine expressed by mast cells, eosinophils, CD4 T lymphocytes, and alveolar macrophages [83, 84]. Its pathway has served as an important inflammatory target in rheumatological conditions and inflammatory bowel disease [85]. Murine studies of allergen-dependent asthma have shown that TNF- α is involved in the recruitment of neutrophils and eosinophils into the airways [86]. Interest in this pathway for asthma further grew as TNF- α expression was demonstrated to be increased in the airways and peripheral blood mononuclear cells of severe asthmatics [87, 88]. TNF- α is associated with neutrophilic inflammation along with AHR, airway remodelling, and glucocorticoid resistance through suppressing glucocorticoid responsiveness and impeding glucocorticoid receptor signalling in asthma [84, 85]. As a result, several inhibitors of the TNF- α pathway have been studied to determine if they play a role in asthma treatment with conflicting results.

Etanercept, a soluble TNF- α receptor fusion protein, initially showed promising effects in two randomized, double-blind, placebo-controlled, parallel-group clinical trials. The first showed that etanercept at a dose of 25 mg twice weekly subcutaneously in corticosteroid refractory asthmatics significantly improved ACQ scores and reduced systemic

inflammation as measured by serum albumin and CRP when compared with placebo [89]. The other etanercept, in refractory asthmatics with high expression of TNF- α , at the same dose and frequency significantly improved lung function (FEV1) and AQLQ scores [88]. However, in a phase 2 double-blind, placebo-controlled trial where 132 patients with moderate-to-severe persistent asthma received the same dose and frequency of etanercept or placebo as the previous clinical trials, etanercept provided no benefit in terms of lung function, ACQ-5 scores, AQLQ scores, or asthma exacerbations when compared with placebo [90].

Infliximab is a chimeric monoclonal antibody that binds to and inactivates TNF- α . Although infliximab had shown to decrease the number of moderate asthmatic patients on ICS with asthma exacerbations, this study has since been retracted due to the concerns about the accuracy of the data and the reliability of the conclusions [91, 92].

Golimumab, a humanized monoclonal anti-TNF- α , at doses of 50, 100, or 200 mg subcutaneously failed to demonstrate efficacy in regard to improving lung function (FEV1) and reducing severe asthma exacerbations in a phase 2 trial involving 309 patients with uncontrolled severe persistent asthma. Although, a post hoc analysis did find that those stratified based on sinusitis and evidence of bronchodilator reversibility ($> 12\%$) had a dose-related (100 mg or 200 mg) decreased in exacerbations. Of note, this trial was terminated early as there was an increased number of adverse events such as infections (tuberculosis, pneumonia, septic shock), cancer (breast cancer, B cell lymphoma, metastatic melanoma, colon cancer, renal carcinoma, cervical carcinoma, and basal cell carcinomas), and death in the golimumab-treated group compared with placebo [93]. Consequently, further evaluation of TNF- α inhibitors in the management of asthma has stopped.

Conclusions

Over the past decade, biologics have provided new hope in treating the challenging subpopulation of severe allergic asthma. However, despite this recent advancement in asthma management, there remains variability in the response of these therapeutics which emphasises the heterogeneous nature of the disease. This review highlights the several advances in the understanding of the pathophysiology of asthma at the molecular level and the resulting emergence of targeted therapy for severe asthmatics with poor disease control despite being maximized on standard therapy (Table 1). It is clearly evident that targeting one cytokine or prostaglandin is not always beneficial for all asthmatics. This finding is in keeping with the estimations that only 1 in 10 drugs that enter phase 1 clinical trials get approval by the FDA [94]. Perhaps the counterargument hinges on the notion that the therapeutics that failed to show efficacy in clinical trials may have not been evaluated in the most appropriate asthmatic subpopulation. Indeed, identifying endotypes through Th2 biomarkers such as serum and sputum eosinophil levels, FeNO levels, and serum periostin levels has been found to be encouraging in determining potential biologic responders. However, this is

Table 1. Biologics evaluated for the treatment of allergic asthma

Name	Type	Target/mechanism of action	Route	Status	Clinical effects
Ligelizumab (QGE031B)	Humanized IgG1 monoclonal antibody	FcεRI *Higher affinity for the IgE receptor than Omalizumab	SC	Discontinued • Phase 2a clinical trial failed to meet the primary objective of demonstrating superiority versus placebo in asthmatic patients	• Inhibits allergen-induced skin test responses • ↓ serum total IgE levels * levels are ↓ to a greater and longer extent than omalizumab in atopic patients
Quilizumab (RG7449)	Humanized IgG1 monoclonal antibody	M1 prime segment of membrane IgE • Targets B lymphocytes before they produce IgE	SC	Discontinued • Phase 2a clinical trials of quilizumab in patients with severe asthma did not show any therapeutic benefit	• Inhibits both the early and late asthmatic responses • ↓ serum total IgE levels
Lumiliximab	Humanized IgG1 monoclonal antibody	CD23	Oral	Discontinued • Phase 2/3 clinical trials did not show any clinical benefit in asthmatic patients	• ↓ serum total IgE levels
Anakinra	Recombinant human IL-1 receptor antagonist	IL-1β	SC	Active • Being assessed in Phase 1/2 clinical trials as a rescue treatment for allergic airway inflammation	
Daclizumab	Humanized IgG1 monoclonal antibody	CD25 • IL-2 receptor alpha-chain of activated lymphocytes	IV	Discontinued • Phase 2 clinical trials had significant adverse events including anaphylactoid reactions and viral meningitis	• ↑ lung function (FEV1) • Improved daytime asthma symptoms • ↑ time to exacerbation • ↓ short-acting beta2-agonist
Pascolizumab	Humanized monoclonal antibody	IL-4 • Prevents IL-4 from binding its receptor	IV	Discontinued • Failed to show efficacy in patients with symptomatic steroid-naïve asthma	
Altrakinept	Soluble	IL-4	Inhaled	Discontinued	Initial clinical trials: • ↑ lung function (FEV1)

Table 1. (Continued)

Name	Type	Target/mechanism of action	Route	Status	Clinical effects
	recombinant human IL-4R			Initial clinical trials were promising but further trials could not demonstrate significant clinical benefit in terms of asthma symptoms and respiratory function (FEV1)	- Improved symptoms ↓ short-acting beta2-agonist ↓ airway inflammation (measured by FeNO)
Lebrikizumab	Humanized IgG4 monoclonal antibody	IL-13	SC	Discontinued Initial clinical trials were promising but Phase 3 clinical trials failed to consistently show significant reduction in asthma exacerbations in high Th2 biomarker patients	Initial clinical trials: ↑ lung function (FEV1) ↓ asthma exacerbations ↓ the late asthmatic response (LAR) * Better responses with higher Th2 biomarkers: total serum IgE (>100 IU/mL), FeNO, blood eosinophil counts ≥140 cells/μL, and periostin levels (≥50 ng/mL)
Anrukinzumab (IMA 638)	Humanized IgG1 monoclonal antibody	IL-13 Allows interaction of IL-13 with IL-13 receptors, but prevents IL-4Rα recruitment to the IL13/IL-13Rα1 complex	SC	Discontinued	↓ both the early and late phase asthmatic FEV1 initially (at 2 weeks)
IMA 026	Humanized IgG1 monoclonal antibody	IL-13 Directly competes with IL-13 in interacting with its receptors (IL13Rα1 and IL13Rα2).	SC	Discontinued	
Dectrekumab (QAX576)	Humanized monoclonal antibody	IL-13	IV	Active Being assessed in Phase 2 clinical trials	
ABT-308	Humanized monoclonal antibody	IL-13	SC	Active Being assessed in Phase 1 clinical trials	

Table 1. (Continued)

Name	Type	Target/mechanism of action	Route	Status	Clinical effects
Pitrakinra (Aerovant)	Recombinant human IL-4 variant	IL-4 and IL-13 • Binds to the heterodimeric IL-4Ra-IL-13Ra1 receptor complex to interfere with the actions of both IL-4 and IL-13	Inhaled	Active • Being assessed in Phase 2 clinical trials	• ↓ the late asthmatic response • ↓ airway inflammation (measured by FeNO) * Better responses with serum eosinophil level of >350 cells/mm³ and upper tertile FeNO (range 20-122 ppb) * Inhaled pitrakinra 10 mg significantly ↓ the number of asthma exacerbations in patients with a specific SNP in the gene encoding IL-4Ra located within the 3' untranslated and proximal region (rs8832GG and rs1029589GG genotypes respectively)
AMG 317	Humanized IgG2 monoclonal antibody	IL-4 and IL-13 • Binds to IL-4Ra to prevent both the binding of IL-4 to its receptor and hinders IL-13 signalling activity	SC	Discontinued • Phase 2 clinical trials failed to show efficacy	Higher dose (300 mg) had: • ↓ asthma exacerbations
Tralokinumab (CAT 354)	Humanized IgG4 monoclonal antibody	IL-13	IV	Discontinued • Initial clinical trials were promising but phase 3 trials had inconsistent findings and failed to show any OCS-sparing potential	• ↑ lung function (FEV1) • ↓ short-acting beta2-agonist • Inconsistent effects on ↓ AAER * Better responses may be achieved with higher biomarkers suggestive of IL-13 activation: higher baseline serum periostin, DPP-4 levels, or FeNO (≥ 37 ppb)
MEDI-528	Humanized IgG1	IL-9	SC	Discontinued • Phase 2 clinical trial failed to demonstrate	• Improved symptoms (non-significant)

Table 1. (Continued)

Name	Type	Target/mechanism of action	Route	Status	Clinical effects
Secukinumab (AIN457)	monoclonal antibody Humanized IgG1 monoclonal antibody	IL-17A		efficacy Discontinued • Terminated at phase 2 clinical trial	• ↓ AAER (non-significant)
Brodalumab (AMG827)	Humanized IgG2 monoclonal antibody	IL-17RA	SC	Discontinued • Phase 2 clinical trial failed to show efficacy	
Risankizumab (Skyrizi)	Humanized IgG1 monoclonal antibody	IL-23A	SC	Active • Being assessed in phase 2 clinical trials	
Etokimab (ANB 020)	Humanized IgG1 monoclonal antibody	IL-33	SC	Active • Being assessed in phase 2 clinical trials	
RG 6149 (AMG 282)	Humanized monoclonal antibody	IL-33	SC or IV	Active • Being assessed in phase 1 clinical trials	
Tezepelumab (AMG 157)	Humanized IgG2λ monoclonal antibody	TSLP	SC	Active • Being assessed in phase 3 clinical trials • OCS-sparing potential also being evaluated	• ↓ early and late asthmatic responses • ↓ systemic and airway inflammation (measured by blood and sputum eosinophils, and FeNO) • ↓ AAER • ↑ asthma control
Timapiprant (OC000459)	Selective CRTH2 (prostaglandin D2 receptor) antagonist	CRTH2	Oral	Active • Being assessed in phase 2 clinical trials	• ↓ late asthmatic responses • ↑ lung function (FEV1) • ↑ quality of life * Better responses may be achieved with atopic subjects with active disease and blood eosinophil counts ≥ 250 cells/μL, and/or

Table 1. (Continued)

Name	Type	Target/mechanism of action	Route	Status	Clinical effects
Fevipiprant	Selective CRTH2 (prostaglandin D2 receptor) antagonist	CRTH2	Oral	Active • Being assessed in phase 3 clinical trials	younger patients (≤ 50 years old) • $\uparrow$ lung function (FEV1) • $\uparrow$ asthma control *Note benefits only obtained in patients with greater severity of airflow limitation (FEV1 $< 70\%$) In eosinophilic asthma (sputum eos $\geq 2\%$): • $\downarrow$ sputum eosinophils • $\uparrow$ asthma control • $\uparrow$ quality of life
GB001 (ADC-3680)	Selective CRTH2 (prostaglandin D2 receptor) antagonist	CRTH2	Oral	Active • Being assessed in phase 2 clinical trials	• $\downarrow$ airway inflammation (measured by FeNO)
MK-1029	Selective CRTH2 (prostaglandin D2 receptor) antagonist	CRTH2	Oral	Active • Being assessed in phase 2 clinical trials	
Setipiprant (ACT-129968)	Selective CRTH2 (prostaglandin D2 receptor) antagonist	CRTH2	Oral	Discontinued** • Failed to demonstrate efficacy in phase 2 clinical trials	• $\downarrow$ late asthmatic responses
Etanercept (Enbrel or Benepali)	Soluble TNF- α receptor fusion protein	TNF- α	SC	Discontinued • Failed to demonstrate efficacy in phase 2 clinical trials	Initial studies: • $\uparrow$ asthma control • $\downarrow$ systemic inflammation (measured by serum albumin and CRP) • $\uparrow$ lung function (FEV1) • $\uparrow$ quality of life
Infliximab (Remicade)	Chimeric IgG1 kappa monoclonal antibody	TNF- α	IV	Discontinued • Phase 2 clinical trial findings retracted over concerns about the	

Table 1. (Continued)

Name	Type	Target/mechanism of action	Route	Status	Clinical effects
Golimumab (CNTO 148 or Simponi)	Humanized IgG1 kappa monoclonal antibody	TNF- α	SC	Discontinued • Failed to show efficacy in phase 2 clinical trials and also terminated early due to significant adverse events	accuracy of the data and the reliability of the conclusions

SC, subcutaneous; IV, intravenous; AAER, annual asthma exacerbation rate; OCS, oral corticosteroid; eos, eosinophils; FEV1, forced expiratory volume in 1 second; CRP, c-reactive protein; TNF- α , tumour necrosis factor alpha; CRTH2, chemoattractant receptor-homologous molecule expressed on TH2 cells; TSLP, thymic stromal lymphopoietin; IL, interleukin; SNP, single nucleotide polymorphisms

**Other selective CRTH2 (prostaglandin D2 receptor) antagonist such as AZD-1981, QAV-680, AZD-5985, AZD-8075, MK-7246, and RG-7185 have been ceased to be further evaluated in asthma

only one piece of the puzzle. Alternatively, targeting multiple components of the inflammatory asthmatic cascade may be more effective than the individual components. Nevertheless, the introduction of biologics has revolutionized the treatment options for asthma, particularly in those suffering from its severe form. As further biologics are developed, emphasis must be made on developing disease-modifying treatments personalized to the patient's form of asthma.

Compliance with Ethical Standards

Conflict of Interest

Anne Ellis has participated in advisory boards for ALK Abello, Circassia Ltd, GlaxoSmithKline, Johnson & Johnson, Merck and Novartis, and has been a speaker for Aralez, AstraZeneca, Boehringer Ingelheim, Meda, Mylan, Merck, Novartis, Pediapharm, Pfizer, and Takeda. Her institution has received research grants from Circassia Ltd, Green Cross Pharmaceuticals, GlaxoSmithKline, Sanofi, Sun Pharma, Merck, Novartis, and Pfizer. Dr. Ellis is also a consultant to Bayer Inc. and reports personal fees from kaleo. Babak Aberumand declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent

This article does not contain any studies with human or animal subjects performed by any of the authors.

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