

Biologics for severe asthma—Which, when and why?

Peer Ameen Shah | Chris Brightling 

Institute for Lung Health, NIHR Biomedical Research Centre, University of Leicester, Leicester, UK

Correspondence

Chris Brightling
Email: ceb17@le.ac.uk

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Abstract

Asthma is a common chronic inflammatory condition of the airways that affects about 350 million people globally. In 5%–10% of individuals, it is severe, with considerable morbidity and high health care utilization. The goal of asthma management is disease control by reducing symptoms and exacerbations and reducing corticosteroid-related morbidity. The era of biologics has revolutionized the management of severe asthma. Biologics have changed our expectations for severe asthma, especially in those people with type-2 mediated immunity. We can now explore the potential for changing disease trajectory and inducing remission. However, biologics are not a panacea for all severe asthma sufferers and despite their success there remains substantial unmet clinical need. We review the pathogenesis of asthma, phenotyping the heterogeneity of asthma, currently licensed and future biologic agents, how to choose the initial biologic, assessing the response, remission and switching of biologic therapies.

KEYWORDS

asthma, asthma control, biologics, biologics switching, biomarkers, exacerbations, remission, severe asthma

INTRODUCTION

Background

Asthma is a common chronic, heterogeneous condition affecting all age groups and is characterized by variable symptoms and variable airflow obstruction.¹ It affects over 350 million people worldwide and is projected to increase to over 400 million by 2025.^{1,2} Approximately 5%–10% of asthmatics have severe disease.^{1–4} According to the ATS/ERS guideline for severe asthma and the Global Initiative (GINA) for Asthma report, when a diagnosis of asthma is confirmed and comorbidities and adherence are addressed, severe asthma is defined as ‘asthma that needs to be treated with high dose inhaled corticosteroids (ICS) plus a second controller (and/or systemic corticosteroids) to prevent it from becoming “uncontrolled,” or that stays “uncontrolled,” despite this treatment’.^{1,3,4}

Severe asthma has the greatest burden of disease with poor asthma control and frequent exacerbations. Severe asthma accounts for more than 50% of the attributable cost of asthma.^{1–4}

Many individuals with severe asthma have frequent short courses of systemic corticosteroids and in some cases

require maintenance oral corticosteroids (OCS). This is associated with high morbidity.⁵ In a large population-based study of adults (<64 years) in the USA, OCS use for fewer than 30 days (20 mg/day) was linked to higher incidence of sepsis, thromboembolism and fracture within 30 days of OCS commencement.⁶ The risk of osteoporosis, fracture, pneumonia, heart failure, cardio-/cerebrovascular disease, type 2 diabetes mellitus, depression/anxiety, cataract, renal impairment and weight gain is significantly increased by taking more than four courses of OCS in a lifetime.⁷

Over the last 25 years, greater understanding has emerged of the clinical features, disordered airway physiology and the underlying immunopathology of severe asthma and how these domains are inter-related. These insights have led to targeted therapies and the new era of biologics. These molecular scalpels have accelerated a major change in our understanding of disease mechanisms, as well as the way we assess and treat patients with severe asthma. Despite these advances, in the clinic it remains challenging to choose which biologic is most appropriate for each patient, what constitutes success to justify continuation and conversely, when to stop or switch therapy.

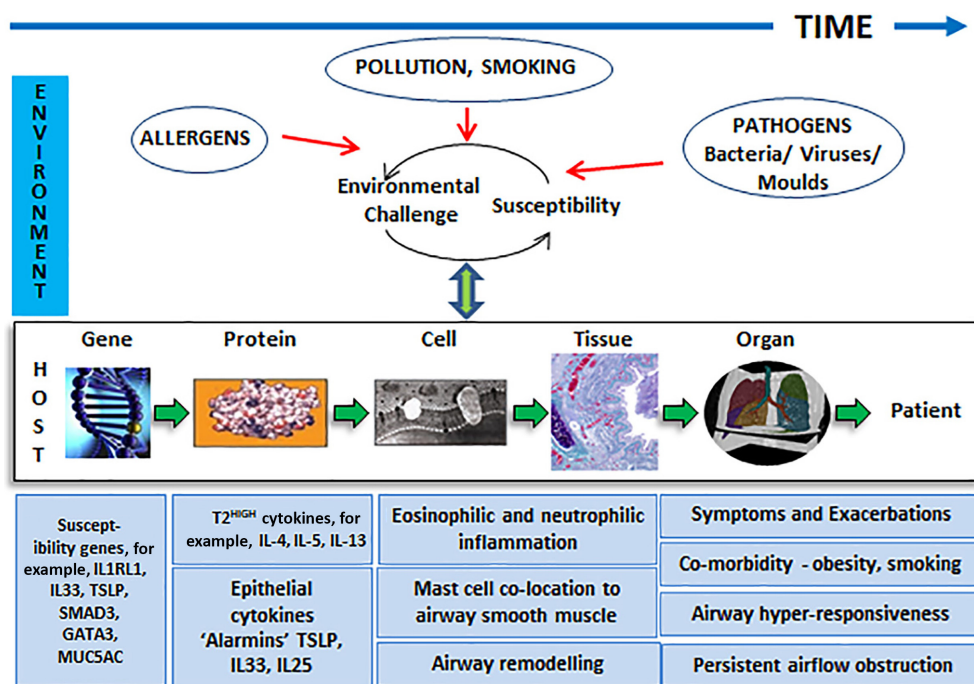


FIGURE 1 Scales of disease of severe asthma with examples of disease heterogeneity that are impacted by host–environment interactions over time.

Pathogenesis of asthma

Understanding the heterogeneity of asthma contributes to better understanding of the disease and provides new therapeutic approaches, particularly for severe asthma.⁸ The phenotype (observable characteristics) and endotype (disease features and their underlying mechanisms) of asthma are complex and represent a variety of host–environment interactions that take place over time and across different spatial scales, from genes to cells to tissue to organ, and are influenced by exposure to allergens, pathogens (viruses, bacteria and fungi) and pollutants like smoke and particulates.^{2,9–12} This paradigm is summarized in Figure 1.

Genome-wide association studies (GWAS) have identified >40 regions of association with asthma. These susceptibility genes include genes for atopy, type-2 mediated inflammation and epithelial injury and repair.^{13,14} Few genetic studies have focussed on moderate-to-severe asthma. The largest study to date by Shrine et al.¹⁵ found substantial shared genetic architecture between mild and moderate-to-severe asthma, as well as reporting for the first time genetic variants associated with the risk of developing moderate-to-severe asthma that regulate mucin production. Additionally, expression quantitative trait loci studies in human bronchial epithelial cells identified risk alleles that regulate expression of genes involved in epithelial function, including *IL-1RL1*, *IL-33*, *TSLP* and *MUC5AC* consistent with epithelial injury, release of alarmins and excess mucus production^{16,17} (Figure 1).

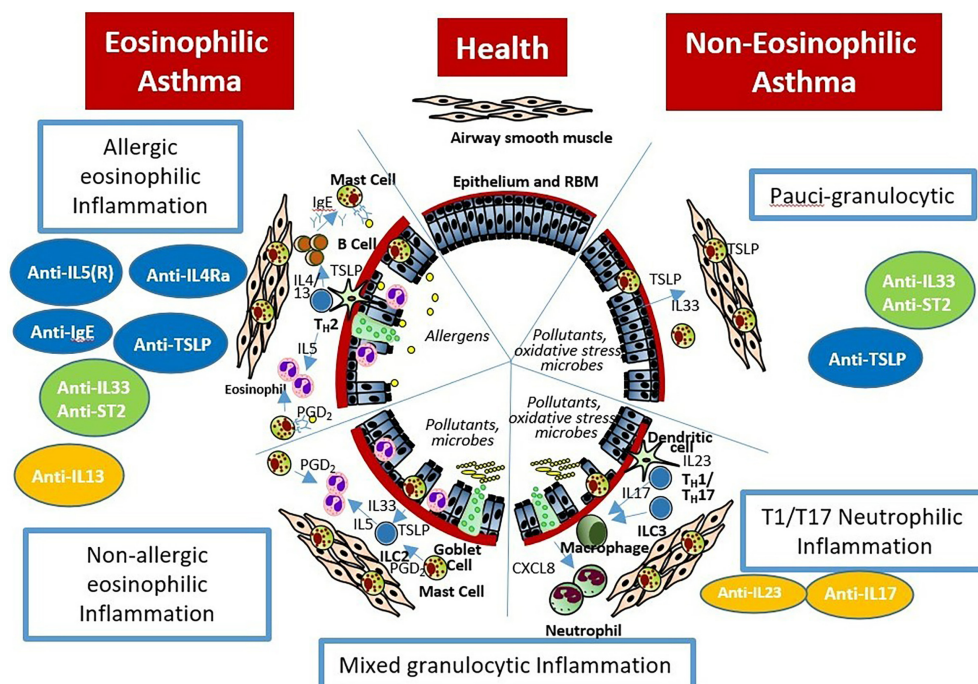
This genetic susceptibility contributes to the underlying airway inflammation which is a hallmark of asthma. In the clinic we have biomarkers to measure type 2-immunity (T2) mediated eosinophilic inflammation including blood eosinophils, fractional exhaled nitric oxide (FeNO), IgE and

(where available) sputum cytology. Sputum cell counts can be used to phenotype patients based on the granulocytic composition of their sputum into eosinophilic, neutrophilic, mixed granulocytic and paucigranulocytic inflammation (Figure 1). The underlying mechanisms driving these inflammatory phenotypes are summarized in Figure 2.

Eosinophilic, T2^{High} airway inflammation is found in more than 50% of asthma patients.^{2,18–20} However, studies on the discontinuation of corticosteroids frequently show emergent eosinophilic airway inflammation, indicating that its prevalence may be underestimated.¹⁹ Atopy is present in 50%–60% of asthmatic adults and children,²¹ but it is more common in children with severe asthma and adults with early-onset disease.²²

In allergic eosinophilic asthma (illustrated in Figure 2), antigen presentation by dendritic cells in the presence of coactivators such as epithelial-derived thymic stromal lymphopoietin (TSLP), leads to naïve T-cell polarization to T2 cells. These T cells become activated, leading to the production of the distinctive T2 cytokines interleukin (IL-)4, IL-5 and IL-13.² In non-allergic eosinophilic asthma (Figure 2), the epithelial derived cytokines or ‘alarmins’ TSLP, IL-25 and IL-33, released after epithelial damage by pollutants and microbes, stimulate type-2 innate lymphoid cells (ILC2), increasing T2 inflammation and up-regulating IL-5 and IL-13.^{9,10} IL-5 is the obligate cytokine for eosinophil survival, maturation and proliferation. IL-4, and to a lesser extent IL-13, play a crucial role by promoting B-cell isotype switching and IgE synthesis. Following cross-linking by the allergen, IgE binds to mast cells with high affinity, which causes mast cell activation. IL-4, IL-13, mast cell-derived prostaglandin D2 and other eosinophil chemoattractants, such as C–C motif chemokine receptor 3 chemokines, are responsible for eosinophil recruitment to the lung mucosa.^{2,9,10,20} IL-13

FIGURE 2 Mechanisms and characteristic pathological features of asthma immunopathology. Features are divided into eosinophilic (allergic and non-allergic), non-eosinophilic (neutrophilic type 1 and type 17 and paucigranulocytic) and mixed granulocytic inflammation. Treatments shaded in blue are licensed therapies with efficacy in asthma; shaded in yellow are treatments that did not demonstrate sufficient benefit in late phase development. Green shading denotes early-to-late phase trials. IL, interleukin; ILC2, type 2 innate lymphoid cells; PDG2, prostaglandin D2; TH, T helper; TSLP, thymic stromal lymphopoietin.



stimulates mucus hypersecretion and induces iNOS in epithelial cells, which results in increases in FeNO.²⁰

Non-eosinophilic, T₂^{low} airway inflammation is less well understood. It is more associated with non-atopic disease with a late onset and poor response to corticosteroids.²³ In some people with severe asthma, T₂^{low} inflammation has been linked to neutrophilic inflammation with activation of T1 and T17 pathways. The cytokines IL-17A, IL-17F and IL-22 generated by T17 cells promote the production of cytokines including IL-6, GM-CSF, CXCL-10 and neutrophil chemokine like CXCL8.^{9,24} Additionally, T₂^{low} disease has also been associated with type 3 innate lymphoid cell activation, which results in the activation of macrophages and the production of neutrophil chemokines (Figure 2).^{2,9}

Biologics targeting T17 pathways have been unsuccessful; indeed anti-IL-23 risankizumab led to a decreased time to asthma worsening compared to placebo, suggesting risankizumab increased susceptibility to poor control in people with severe asthma. Gene expression pathway analysis demonstrated that anti-IL-23 downregulated T1 and T17 transcription factors, perforin and granzyme expression consistent with increased risk of infection.²⁵ Importantly, neutrophilic airway inflammation could indicate bacterial colonization or the effects of corticosteroids on promoting neutrophil survival and suppressing T2 immunity, upregulating type 1 or type 17 immunity.²

The pathophysiology of obesity-related asthma has also been linked to TH17 and IL-6. IL-6 also contributes to systemic inflammation in patients with more severe asthma and obesity.²⁶ Intriguingly, people with severe asthma and obesity also have elevated levels of submucosal eosinophils^{27,28} possibly due to altered survival of eosinophils in the lung.²⁹

Paucigranulocytic T₂^{low} asthma in some people with severe asthma reflects that their underlying T2 inflammation is well-controlled with treatment. Indeed the absence of T2 inflammation with low blood eosinophils and low FeNO represents a low risk group.³⁰ However, persistent symptoms and airflow obstruction can occur in this group of people with severe asthma and might reflect features that are observed both in T₂^{high} asthma and beyond T2-mediated disease, such as epithelial injury and release of epithelial derived cytokines.

The underlying genetic susceptibility and inflammatory milieu including both T2 inflammation and mechanisms beyond T2 just described, together with airway remodelling contributes to the consequent disordered airway physiology in asthma with variable or persistent airflow obstruction³¹ and airway hyperresponsiveness.

Airway remodelling describes changes in the airway structure including epithelial damage leading to goblet cell and mucous gland hyperplasia, ciliary dyskinesia and consequent mucus plugging. Advances in semi-quantitative scoring of mucus plugging by CT has led to improved assessment and³² underscored that mucus plugging is associated with eosinophilic T2 inflammation. In observational studies anti-IL-5 therapies have reduced mucus plugging³³ and anti-TSLP in a randomized placebo-controlled trial demonstrated reduction in mucus plugging which was associated with baseline eosinophilic inflammation.³⁴ Additionally, there is sub-epithelial collagen deposition, an increase in the number of myofibroblasts and fibrocytes, as well as airway smooth muscle hyperplasia and hypertrophy.³⁵ The strongest predictors of airflow limitation are increased airway smooth muscle mass and increased sub-epithelial fibroblasts.^{36,37} These remodelling changes result in thickening of the airway wall and luminal constriction visible on quantitative CT.³⁸ In

TABLE 1 Biologic therapies against severe asthma based on Global Initiative for Asthma 2022¹

Biologic (target)	Omalizumab (IgE)	Mepolizumab (IL-5)	Reslizumab (IL-5)	Benralizumab (IL-5Rα)	Dupilumab (IL-4Rα)	Tezepelumab (TSLP)
Age	≥6 years	≥12 years	≥18 years	≥18 years	≥12 years	≥12 years
Mode of administration	Subcutaneous injection	Subcutaneous injection	Intravenous infusion	Subcutaneous injection	Subcutaneous injection	Subcutaneous injection
Dosage	75–600 mg SC (based on weight and tot IgE) every 2 or 4 weeks	100 mg SC every 4 weeks in ≥12 years old, 40 mg every 4 weeks in ages 6–11 years	3 mg/kg IV every 4 weeks	30 mg SC every 4 week for first 3 doses, followed by 30 mg every 8 weeks	200 mg or 300 mg (OCS-dependent or comorbidities) every 2 weeks	210 mg every 4 weeks
GINA Eligibility criteria—Severe asthma with	Severe exacerbations within last year, sensitization to inhaled allergens, total serum IgE and weight within local dosing range	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL or ≥300 cells/μL (locally specified)	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL or ≥300 cells/μL (locally specified)	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL or ≥300 cells/μL (locally specified)	Severe exacerbations within last year, blood eosinophil ≥150 cells/μL and ≤1500 cells/μL, or FeNO ≥25 ppb, or maintenance OCS	Severe exacerbations within last year
Additional use	Nasal polyposis, chronic idiopathic urticaria	Nasal polyposis, EGPA, hyper eosinophilic syndrome		EGPA, hyper eosinophilic syndrome	Moderate–severe atopic dermatitis, CRS and nasal polyposis	With or without elevated T2 markers
Expected outcomes ↑↕↔	Severe exacerbations↓ Quality-of-life↑ Symptom control↑ Lung function↔ OCS reduction↔ (possible benefit)	Severe exacerbations↓ Quality-of-life↑ Symptom control↑ Lung function↑ OCS reduction↓	Severe exacerbations↓ Quality-of-life↑ Symptom control↑ Lung function↑ OCS reduction (not tested)	Severe exacerbations↓ Quality-of-life↑ Symptom control↑ Lung function↑ OCS reduction↓	Severe exacerbations↓ Quality-of-life↑ Symptom control↑ Lung function↑ OCS reduction↓	Severe exacerbations↓ Quality-of-life↑ Symptom control↑ Lung function↑ OCS reduction↔ (possible benefit in eosinophilic pts)
Predictors of good response	Blood eosinophils ≥260 cells/μL, FeNO ≥20 ppb. Childhood-onset asthma, allergen-driven symptoms	Higher blood eosinophils, higher number of severe exacerbations in the previous year, nasal polyposis, maintenance OCS at baseline	Adult-onset asthma	Higher blood eosinophils, higher number of severe exacerbations in the previous year, nasal polyposis, maintenance OCS at baseline, lower lung function FEV1 %59>	Higher blood eosinophils, higher FeNO	Higher blood eosinophils, higher FeNO, although some benefit in those T2 low asthma

experimental studies, targeting IL-13 and TSLP has led to an increase in the size of the airway lumen.^{39–41}

Airway hyperresponsiveness results from increased airway smooth muscle contraction that can occur in response to direct or indirect stimuli and is independent of the underlying inflammatory profile.^{9,42} Asthma patients have higher levels of mast-cell infiltration into the airway smooth muscle than healthy people and patients with eosinophilic bronchitis but without airway hyperresponsiveness. The degree of airway smooth muscle infiltration by mast cells is related to the severity of airway hyperresponsiveness.^{43,44} These mast cells release mediators such as histamine, PGD₂ and cysteinyl leukotrienes, which results in contraction of airway smooth muscle. Additionally, they release T₂ cytokines IL-4 and IL-13.⁹ IL-13 leads to activation of airway smooth muscle cells with altered ASM tone, airway hyperresponsiveness and bronchoconstriction. The epithelial derived cytokines IL-33 and TSLP can activate mast cells leading to cytokine release and promoting airway smooth muscle contraction.⁴⁵ In experimental studies, TSLP blockade has consistently led to an improvement in airway hyperresponsiveness following allergen, methacholine and mannitol challenges.^{41,46,47}

Currently licensed and future biologics

Severe asthma patients who experience frequent exacerbations, have poor symptom control or are OCS-dependent should be considered for further biologic therapy.¹ The six currently available biologics all successfully target eosinophilic T₂^{high} severe asthma. In contrast to the failure of T₁₇, IL-23 and anti-neutrophil targeted therapies, targeting the epithelial-derived cytokines has demonstrated benefit in those with eosinophilic T₂^{high} and non-eosinophilic T₂^{low} asthma as illustrated in Figure 2. The indications, route of administration and likely outcomes for these licensed biologics are summarized in Table 1.

There are no head-to-head randomized controlled trials (RCTs) comparing these biologics for severe asthma, resulting in a paucity of high level evidence to support and guide clinical decision making.²⁰ Eligibility for biologic therapy is dependent upon licensing criteria, local payer criteria and affordability, which are different between regions and countries. Eligibility includes age, the number of exacerbations in the previous year, regular OCS use, asthma control, quality of life, lung function, biomarkers (blood eosinophil count, FeNO and serum total and allergen-specific IgE) and comorbidities (e.g., nasal polyposis, atopic dermatitis) together with cost. Patient preference should always be considered and might be further informed by dosing frequency and route of delivery.^{1,20}

Anti-IgE: Omalizumab

Anti-IgE omalizumab, was the first biological medication to be authorized for the treatment of asthma. It is approved for

use in people with moderate to severe atopic asthma who are at least 6 years old and are sensitized to aeroallergens.¹ Omalizumab inhibits IgE and prevents it from attaching to mast cells, basophils and dendritic cells' high- and low-affinity receptors. This results in receptor downregulation and a decrease in the downstream recruitment of inflammatory cells.¹⁰ A systematic review of five RCTs showed that it causes a 44% decrease in severe exacerbations and improves quality of life in adults and children.⁴⁸ Likewise, a meta-analysis evaluating real-world effectiveness of omalizumab showed a 41% reduction in percentage of patients receiving maintenance OCS at 12 months compared with baseline.⁴⁹ A treatment response is not predicted by serum IgE levels,^{50,51} but a post hoc analysis of an observational study showed that a greater decrease in exacerbations was observed in patients with blood eosinophils ≥ 260 cells/ μ L or FeNO ≥ 20 ppb.^{52,53}

In contrast, the STELLAIR study reported that omalizumab was effective in treating children and adolescents, and adults with eosinophil counts below 150 cells/ μ L, with 57.7% of patients meeting the definition of a responder based on Global evaluation of treatment effectiveness (GETE) (physician's evaluation) and a 40% decrease in the annual exacerbation rate.⁵⁴ In patients with severe chronic rhinosinusitis and nasal polyps, omalizumab improved outcomes.⁵⁵ According to the EXPECT trial, there was no evidence that receiving omalizumab during pregnancy increased the incidence of serious congenital abnormalities.⁵⁶

Anti-IL5: Mepolizumab and reslizumab

Mepolizumab is an anti-IL-5 biologic licensed for use as add-on therapy for severe eosinophilic asthma in patients aged 12 years or older.¹ This monoclonal antibody binds with high affinity to IL-5, blocking interaction with the IL-5 receptor expressed by eosinophils and basophils.⁵⁷ Consequently there is a marked reduction in eosinophilic inflammation but no effect on FeNO.⁵⁸ A systematic review of three RCTs found that treatment with mepolizumab in severe eosinophilic asthma results in a 51% decrease in severe exacerbations and reduces the daily maintenance OCS by 50%.^{59,60} Additionally, mepolizumab improves lung function, quality of life, and asthma control, albeit to a modest degree. A post hoc meta-analysis of the relationship between blood eosinophil count and mepolizumab treatment response in severe eosinophilic asthma revealed that mepolizumab consistently produced clinical benefits in patients with baseline blood eosinophil counts ≥ 150 cells/ μ L, and the treatment response was greater with increasing blood eosinophil counts.⁶¹ In the first placebo-controlled randomized trial of children and adolescents receiving high to very high dose ICS with exacerbation prone asthma, the MUPPITS-2 trial demonstrated a rate reduction of 27% in exacerbations in those receiving mepolizumab versus placebo.⁶² However, in this study there was no benefit demonstrated for asthma control, nor lung function. Mepolizumab has also demonstrated benefits in people with refractory

severe chronic rhinosinusitis with nasal polyps⁶³ and in those with eosinophilic granulomatosis with polyangiitis (EGPA)⁶⁴ and hypereosinophilic syndrome.⁶⁵

Reslizumab is an anti-IL-5 biologic approved for use as an adjunctive treatment for severe eosinophilic asthma in individuals 18 years of age or older as an intravenous infusion.^{1,66} A systematic review of five RCTs found that intravenous reslizumab use in severe eosinophilic asthma results in a 54% decrease in severe exacerbations.⁵⁹ In contrast, two phase 3, randomized, double-blind, placebo-controlled studies of subcutaneous reslizumab were ineffective in lowering the number of exacerbations or the daily maintenance dose of OCS.⁶⁷

Anti IL5R: Benralizumab

Benralizumab is approved for use as an adjunctive treatment for severe eosinophilic asthma in individuals who are 18 years of age or older.¹ Benralizumab binds to IL-5R α , thereby preventing the interaction between IL-5 and its receptor and promotes antibody-dependent cell-mediated cytotoxicity enhancing eosinophil apoptosis.⁶⁸ Similar to the IL-5 neutralizing biologics, benralizumab results in profound reductions in eosinophilic inflammation without affecting FeNO.⁵⁸ A systematic review of three RCTs found that benralizumab use in severe eosinophilic asthma results in a 47% decrease in severe exacerbations and reduced daily maintenance OCS use.⁵⁹ A level of blood eosinophils $\geq 300/\mu\text{L}$, maintenance OCS use, history of nasal polyposis and FVC $< 65\%$ of predicted have been identified as indicators of enhanced benralizumab efficacy.^{69,70}

The PONENTE study subgroup analysis showed that treatment with benralizumab reduced the dosage of OCS regardless of baseline eosinophil count, OCS dosage or length of OCS treatment.⁷¹ Benralizumab led to improvements in patients with EGPA⁷² and hypereosinophilic syndrome.⁷³ Even though benralizumab has shown some benefits in severe chronic rhinosinusitis with nasal polyps⁷⁴ the evidence has not supported a licence for this indication. No increase in serious infection risk has been observed in those treated with benralizumab for up to 5 years.⁷⁵

Anti-IL-4R: Dupilumab

Dupilumab is approved for use as an adjunctive treatment for severe eosinophilic asthma in individuals who are 12 years of age or older.¹ Dupilumab binds to IL-4R, blocking the signalling of both IL-4 and IL-13.⁷⁶ A systematic review of three RCTs found that dupilumab use in severe eosinophilic asthma results in a 56% decrease in severe exacerbations, reduced daily maintenance OCS use and improved lung function.⁵⁹ Dupilumab is most effective in reducing exacerbations in those with a type 2 inflammatory phenotype with either or both of blood eosinophils > 150 cells/ μL or FeNO > 25 ppb,⁷⁷ whereas reduction in OCS was achieved independent of baseline T2 biomarkers.⁷⁸ The TRAVERSE study revealed that adult and adolescent

patients with moderate-to-severe asthma had persistent improvements in clinical efficacy for up to 148 weeks.⁷⁷

Dupilumab reduces FeNO and total IgE, while blood eosinophil counts initially increase, then decrease to levels comparable or below baseline over a year.⁷⁷ In children with moderate-to-severe asthma, dupilumab reduced the annualized severe asthma exacerbations by 59% and improved asthma control and lung function compared to placebo.⁷⁹ Dupilumab has also demonstrated marked benefit in atopic dermatitis,⁸⁰ and severe chronic rhinosinusitis with nasal polyps.⁸¹

Anti-TSLP: Tezepelumab

Tezepelumab is approved for use as an adjunctive treatment for severe asthma in individuals who are 12 years of age or older.¹ Tezepelumab binds to TSLP, thus preventing its interaction with TSLP receptor complex.⁸² In the phase 2b PATHWAY and phase 3 NAVIGATOR studies, tezepelumab reduced the asthma exacerbation rate by 71% and 56%, respectively, compared with placebo in patients with severe, uncontrolled asthma.^{83,84} A reduction in exacerbations was observed in patients with either high or low levels of T2 inflammation biomarkers (blood eosinophils and FeNO), although the magnitude of exacerbation reductions was greater among those with high levels of T2 biomarkers. Baseline blood TSLP did not predict the likelihood of response.⁸⁵ Tezepelumab decreases the T2 biomarkers blood eosinophil count, FeNO and serum total IgE. In a post hoc pooled analysis of those patients with both a low blood eosinophil count and FeNO, the exacerbation rate reduction was 35% in those receiving tezepelumab versus placebo, excluding patients who are on maintenance OCS. However, the confidence intervals were wide due to the limited number of subjects in this subgroup analysis.⁸⁶

In addition to its beneficial impact on exacerbations, tezepelumab also improved asthma control, health status, lung function and has consistent beneficial effects on airway hyperresponsiveness.^{41,46,47} In the corticosteroid reduction study SOURCE, a significant reduction in OCS dose with tezepelumab versus placebo in the overall population was not observed, although in a secondary analysis there was benefit for participants with baseline blood eosinophil counts ≥ 150 cells/ μL .⁸⁷

Participants from the NAVIGATOR and SOURCE studies were invited to participate in the DESTINATION study, a randomized, double-blind, placebo-controlled and long-term extension study. DESTINATION showed that tezepelumab treatment was well tolerated for up to 2 years and led to sustained reductions in asthma exacerbations, with improvements in asthma control and lung function.⁸⁸

Anti-IL-33 and anti-Anti-ST2

Biologics targeting the epithelial derived cytokine IL-33 and its cognate receptor ST2 are not licensed therapies. Itepekimab is a monoclonal antibody against IL-33. In a phase

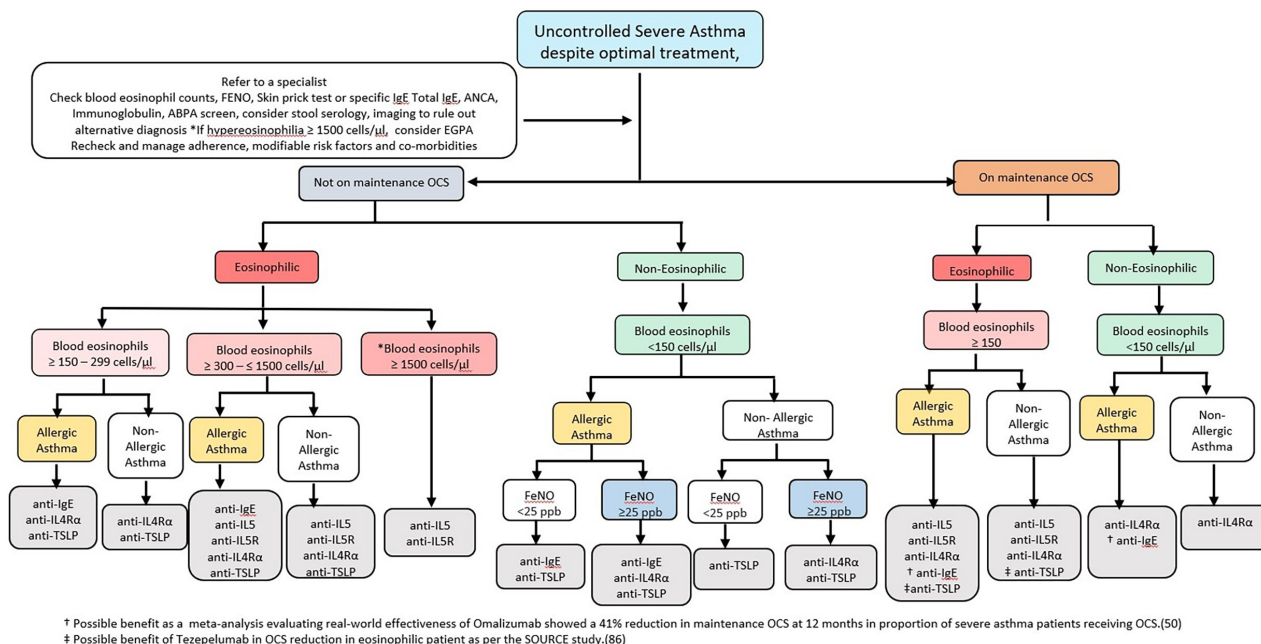


FIGURE 3 Algorithm for choosing biologic therapy.

2 trial, it improved asthma control and quality of life in adults with moderate-to-severe asthma. Itepekimab in combination with dupilumab did not lead to additional benefit compared to dupilumab alone.⁸⁹ Astegolimab is a monoclonal antibody that selectively inhibits ST2 (the IL-33 receptor). A double-blind, placebo-controlled, dose-ranging study (ZENYATTA) in patients with uncontrolled severe asthma demonstrated that Astegolimab reduced asthma exacerbations versus placebo with notably greater reductions in those with low blood eosinophil counts.⁹⁰

Indications of biologics – What to choose first in the clinic

All of the licensed biologics—omalizumab, mepolizumab, reslizumab, benralizumab, dupilumab and tezepelumab—are prescribed as an adjunctive therapy for people with severe asthma who frequently experience exacerbations and show signs of T2 inflammation. Tezepelumab is also recommended for treatment in those without T2 airway inflammation.¹ Additionally, biologics are prescribed to enable OCS step-down to reduce future risk of corticosteroid associated morbidity.

The GINA specific eligibility requirements for each biologic are described in Table 1. The algorithm shown in Figure 3 provides a possible decision tree for which biologic to start with based on current therapy, inflammatory biomarkers (blood eosinophils and FeNO) and allergic disease. This decision tree is based on current evidence and assumes equal access to all licensed biologics; it does not take into account patient preference, route of administration, dosing frequency nor cost.

Predictive phenotypic characteristics and biomarkers of likely success of a biologic are needed to determine both likely benefit but also to help choose the most appropriate biologic for an individual. Known predictors of response are described in Table 1. With all of the currently licensed biologics the greatest benefit is observed in those with higher blood eosinophils. For anti-IL-4Rα and anti-TSLP, FeNO as a marker of T2^{high} asthma is also a predictor of greater response either alone or together with increased blood eosinophils. Presence of allergic driven disease is required to prescribe anti-IgE, but the level of IgE is not a predictor of response. Atopy and presence of allergic disease does not provide additional prediction of response beyond blood eosinophils and FeNO for other biologics.

The benefit from omalizumab and dupilumab appears considerably greater than biologics targeting IL-5 in children and adolescents, although head-to-head trials in this age group are lacking and mepolizumab has some demonstrated efficacy. Similarly, anti-IL-5 biologics appear to have greater benefit in those with adult rather than childhood-onset asthma. Some post hoc analyses of response to biologics have identified other possible predictive features such as presence of nasal polyposis, maintenance OCS and impaired lung function predicting greater response to benralizumab.^{70,91,92}

The magnitude of improvement in asthma control and lung function is consistently different between biologic studies, with modest improvements following anti-IL-5 and notably greater improvements with anti-IL-4Rα and anti-TSLP. However, whether clinical features and lung function predict response to biologics have not been rigorously tested in prospective studies. Some biologics share additional licensed indications. If the rationale for starting a biologic is to manage more than one licensed indication then choosing

the biologic that is appropriate for more than one indication is preferable, such as severe asthma and EGPA for anti-IL-5 or severe asthma and atopic dermatitis for anti-IL-4R α .

The eligibility requirements for local payers vary considerably from country to country; not all biologics are accessible in every country. For example, in the UK the National Institute for Health and Care Excellence (NICE) recommends omalizumab as an adjunctive to optimized standard therapy for children (≥ 6 years). Adults with poorly controlled allergic IgE-mediated severe asthma who require continuous or frequent treatment with systemic corticosteroids (at least four exacerbations) in the previous year are eligible if the manufacturer makes omalizumab available with the discount agreed in the patient access scheme.⁹³ Mepolizumab and benralizumab are recommended by NICE as an adjunctive to optimized standard therapy for adults with poorly controlled severe eosinophilic asthma who have had blood eosinophils ≥ 300 cells/ μ L and at least four exacerbations requiring systemic corticosteroids within the previous year, or has had maintenance OCS equivalent to prednisolone 5 mg/day for the previous 6 months, or if blood eosinophils are ≥ 400 cells/ μ L, then at least three exacerbations requiring systemic corticosteroids during the past year. The manufacturer must provide it according to the commercial arrangement.^{94,95}

Reslizumab is recommended by NICE as an adjunctive to optimized standard therapy for adults with poorly controlled severe eosinophilic asthma who have had at least three exacerbations requiring systemic corticosteroids within the previous year with blood eosinophils ≥ 400 cells/ μ L, and the company provides reslizumab with the discount agreed in the patient access scheme.⁹⁶ NICE recommends dupilumab as an adjunctive to optimized standard therapy for adolescents (≥ 12 years) and adults with poorly controlled severe asthma with type 2 inflammation who have had at least four exacerbations necessitating systemic corticosteroids within the previous year, and have blood eosinophils ≥ 150 cells/ μ L, FENO ≥ 25 ppb and are ineligible for mepolizumab, reslizumab or benralizumab, or did not have adequate response to these biologics and the manufacturer provides dupilumab according to the commercial arrangement.⁹⁷ NICE is evaluating tezepelumab approval for treating severe asthma.⁹⁸

In Australia, there are four biologic therapies (omalizumab, mepolizumab, benralizumab and dupilumab) that can be used to treat severe asthma uncontrolled despite optimized management.⁹⁹ The National Asthma Council Australia recommends omalizumab as an adjunctive therapy for children (≥ 6 years) and adults with uncontrolled allergic IgE-mediated severe asthma who have total serum IgE ≥ 30 IU/mL and evidence of atopy (skin prick testing or specific IgE) in the last 12 months.⁹⁹ It also recommends mepolizumab and benralizumab as an adjunctive therapy for uncontrolled severe eosinophilic asthma in adults and adolescents ≥ 12 years with blood eosinophils ≥ 300 cells/ μ L, or blood eosinophils ≥ 150 cells/ μ L if on maintenance OCS in the last 12 months. Dupilumab is recommended as an adjunctive treatment for uncontrolled severe eosinophilic or

allergic asthma in adults and adolescents ≥ 12 years with blood eosinophils ≥ 300 cells/ μ L or blood eosinophils ≥ 150 cells/ μ L if on maintenance OCS, or total serum IgE levels above 30 IU/mL with evidence of atopy (skin prick testing or specific IgE) within the previous 12 months.⁹⁹

Biologic success and remission

The aim of asthma treatment is to achieve disease control and reduce future risk. Thus, the current focus is on symptom control, exacerbation reduction and elimination of the use of regular OCS. In clinical trials, various definitions of response to biologic therapy and outcome measures have been used, as described in the systematic review by Rattu and colleagues.¹⁰⁰ This makes it difficult to reach firm conclusions about the relative efficacy of various biological agents, especially given the lack of head-to-head comparison studies.¹⁰¹

In a multi-step consensus process, the COMSA (Core Outcome Measures sets for paediatric and adult Severe Asthma) working group involving four key stakeholder groups (Paediatric and adult patient representatives with severe asthma, Paediatric and adult respiratory clinicians, pharmaceutical representatives and health regulators) developed pan-European consensus patient-centred core outcome measures (COM) sets for use in studies of biological therapies in paediatric (children and adolescents) and adult patients with severe asthma. The outcomes are described in Table 2. This will enable data synthesis and biologics evaluation in clinical studies of paediatric and adult asthma, as well as standardize outcome reporting for severe asthma biological trials.¹⁰¹

Using a modified Delphi method, 81 experts from 24 countries reached a consensus on the definition of a severe asthma super-responder¹⁰²: namely, the patient must have met all three major criteria in the last 12 months, or two major criterion and one minor one. The major criteria are no asthma exacerbation, major improvement in asthma control (1 or more reduction in ACQ score, improvement of 6 or more in ACT) and no use of maintenance OCS or weaning to adrenal insufficiency. Minor criteria are 75% reduction in exacerbation, well controlled asthma (ACQ < 1 or ACT > 19) and an improvement of 500 mL or more in FEV1. If there is no asthma exacerbation, then 75% exacerbation reduction should not be counted as an additional minor criterion.¹⁰²

Biological therapy also allows us to consider whether we can raise our ambition towards asthma remission. Clinical experts in asthma developed a framework for asthma remission as a treatment goal using a modified Delphi approach that is in line with accepted definitions of remission in other chronic inflammatory diseases.¹⁰³ Asthma remission includes disease control, no use of systemic corticosteroid therapy for long-term disease management or exacerbation treatment over the last 12 months or more, and normalization or at least optimisation of lung function. Remission can

TABLE 2 Core outcome measures sets for paediatric and adult severe asthma (COMSA).¹⁰¹

Core Outcome Measures (COM) sets	Adult (≥18 years)	Paediatric (children and adolescents aged 6–17 years)
Clinical outcome measures	Forced expiratory volume in 1 second (FEV1) as z scores	Forced expiratory volume in 1 second (FEV1) as z scores
Healthcare resource use	Annual frequency of severe exacerbations ^a	Annual frequency of severe exacerbations ^a
Healthcare resource use	Maintenance oral corticosteroid use	Maintenance oral corticosteroid use
Asthma control outcome measures	Asthma Control Questionnaire-6 ^b	Asthma Control Test (ACT) or Childhood-ACT
Asthma-specific quality of life questionnaires	Severe Asthma Questionnaire	Paediatric Asthma Quality of Life Questionnaire

^aSevere exacerbation defined as events requiring systemic corticosteroids for ≥3 days and/or a hospitalization/emergency room visit for asthma requiring systemic corticosteroids.

^bSymptoms and rescue medication use reported separately.

TABLE 3 Remission on biologics.

Post hoc analysis	Biologic	Remission definition used	Remission with the biologic
Real-World REDES Study ¹⁰⁶	Mepolizumab	OCS-free, exacerbation-free and asthma control ACT score ≥20	37% at 12 months
SIROCCO, CALIMA, ZONDA ¹⁰⁴	Benralizumab	Zero exacerbations, zero OCS use, ACQ-6 score ≤0.75 and pre-bronchodilator FEV1 increase ≥100 mL	14.5% at 12 months
LIBERTY ASTHMA QUEST ¹⁰⁵	Dupilumab	No exacerbations, ACQ-5 <1.5, post bronchodilator FEV1 >80%	29.6% (24 weeks) 20.1% at 52 weeks
NAVIGATOR study ¹⁰⁷	Tezepelumab	ACQ-6 ≤0.75, no OCS use, no exacerbation, improvement in pre-BD FEV1 >20% or pre-BD FEV1 >80% at 52 weeks	12.7%

be with or without maintenance therapy. Even if this clinical remission is achieved, in some there remains underlying inflammation that increases the risk of relapse and thus complete remission has been considered to also include normalization of the underlying inflammatory biomarkers.

Post hoc analysis of late-phase studies and real-world effectiveness studies have investigated whether biologics can induce clinical remission.^{104–107}

These studies are summarized in Table 3. Critically, these studies use different definitions for remission. Therefore they not head-to-head and the different outcome measures make cross-comparisons impossible. Standardized endpoints using COM are required and further studies of biomarkers to predict response are urgently needed if we are to progress towards precision medicine for individualized management.

In the real world, clinical decisions need to be made with patients on an individual basis. Before starting a biologic it is critical to confirm the diagnosis, optimize treatment and adherence and optimize management of comorbidities and triggers. As already noted eligibility for a biologic needs to be confirmed based on licensing criteria and local healthcare system criteria. Patient phenotyping including the measurement of inflammatory biomarkers (blood eosinophils, FeNO and sputum cytology where available) is essential in choosing an appropriate biologic for that individual. The route of administration and dosing regimen also needs to be considered. Subcutaneous administration will typically be preferred to intravenous and patients are likely to want less frequent

dosing regimens, although this has become less important as many of the biologics can be administered (or self-administered) in the patient's home.

To determine if a biologic is sufficiently successful to be continued, most health care systems have set parameters for response. These include health economic considerations which are greatly influenced by cost drivers such as hospitalisations and health care utilization, rather than symptom burden. According to NICE UK, an adequate response is one that maintains or improves asthma control after a year by showing a clinically significant reduction (50%) in the number of severe exacerbations and/or a clinically significant reduction (50%) in maintenance OCS.^{94–97}

Whilst patients are receiving biological therapy it is important to regularly assess response. For example, a note of caution is that some patients have demonstrable early benefit that might give them the impression that they can reduce their inhaled corticosteroid medication. Encouraging continued use of regular medication and inhaler technique is important. Reduced adherence to ICS can lead to increase FeNO which can be used as a biomarker of poor adherence.¹⁰⁸

Failure to meet the criteria for response and possible discontinuation of the biologic suggests that the patient's symptoms and exacerbations are driven by other mechanisms. This includes comorbid conditions such as dysfunctional breathing, vocal cord dysfunction and recurrent infection.^{109–111} Autoantibodies to the biologic¹¹² or underlying auto-immunity¹¹³ might also attenuate clinical

response to biologics in some cases. The reason for failure to respond adequately needs to be considered carefully in each patient, as the reason might also affect the likelihood of response to other biologics. Before switching, likely reasons for failure should be carefully assessed, to determine the next best and available biologic.

There are limited, poor quality data on biologic switching. Real world biologic use data in adults with severe asthma from 2015 to 2020 from 11 countries showed that omalizumab was the most common initial biologic in 2015 and benralizumab in 2019, followed by mepolizumab and dupilumab.¹¹⁴ While 79% patients continued their first biologic, 10.2% stopped and 10.8% were switched to another biologic.¹¹⁴ The most common first switch was from omalizumab to an anti-IL-5/5R with subsequent switch to another anti-IL-5/5R.¹¹⁴ These biologic drugs were stopped or switched due to unfavourable side effects or lack of efficacy.¹¹⁴ Those who switched received their initial biologic with median durations of 6.8 months for omalizumab, 4.3 months for mepolizumab and 6.0 months for benralizumab.¹¹⁴

Importantly, the criteria of either or both a 50% reduction in exacerbations and a 50% reduction in maintenance OCS supports decision making for continuation of a biologic, but does not necessarily translate into good control for some individuals. For example, a patient with poor control of asthma symptoms, impaired quality of life and eight exacerbations in the year prior to starting a biologic would be considered a 'biologic-success' if they still had four exacerbations and persistent symptoms after a year of treatment with a biologic. Therefore to raise our future ambition towards remission, we will need to consider not only relative reduction in exacerbations and oral corticosteroid use but individualized treatment goals that include all the dimensions of the disease.

CONCLUSION

The era of biologics has revolutionized the management of severe asthma. The use of immunomodulatory therapies with substantial side-effects such as cyclosporine and methotrexate has been consigned to history and maintenance OCS can also be eradicated as part of the standard of care for severe asthma. Biologics have changed our expectations for severe asthma and mean we can now explore the potential for changing the disease trajectory and inducing remission.

Even though there is good reason to be optimistic, biologics are not the panacea for severe asthma in many patients in whom symptoms, exacerbations and lung function impairment remain. Thus although wider availability of current biologics are needed, additional pharmacological and non-pharmacological interventions are still required. Careful phenotypic assessment of patients including current and novel predictive biomarkers will help to choose the best biologic for each patient and guide decisions on early switching if required. We are progressing to a precision medicine future for severe asthma.

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CONFLICTS OF INTEREST STATEMENT

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ORCID

Chris Brightling  <https://orcid.org/0000-0002-9345-4903>

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AUTHOR BIOGRAPHIES

Peer Ameen Shah is a Clinical Research Fellow at NIHR Respiratory Biomedical Research Centre, Glenfield Hospital Leicester and a respiratory specialty trainee (ST6). His main research focus is on understanding asthma remission and improving the clinical management of asthma. He is also a member of the British Thoracic Society and European Respiratory Society.

Chris Brightling is a Fellow of the Academy of Medical Sciences, National Institute for Health Research Senior Investigator, Respiratory Theme Lead for Leicester NIHR Biomedical Research Centre, Director Institute for Lung Health, Director For the Institute for Precision Health and Honorary Consultant Respiratory Physician, Leicester, UK. His main research focus is on improving the clinical management and understanding the immunopathogenesis of asthma, chronic cough, COPD and long-COVID. He is a member of the Global Initiative for Asthma—GINA scientific committee.

SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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