



Biologic treatment options for severe asthma

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Asthma is a common condition that causes episodic expiratory airflow limitation due to bronchial smooth muscle constriction and airways inflammation resulting in increased respiratory symptoms and acute asthma exacerbations. Patients with severe asthma have relied on either recurrent courses or daily use of oral corticosteroids (OCS) to control their disease. However a high level of OCS exposure is associated with significant morbidity and mortality. In recent years the elucidation of the role of T2 inflammation underpinning asthma pathogenesis has led to the development of monoclonal antibody (mAb) therapies targeting this pathway. Established therapies now include omalizumab targeting IgE, mepolizumab and reslizumab targeting IL-5, benralizumab targeting the IL-5R and dupilumab targeting IL-4R. For many patients these therapies have been transformative and their use has additionally advanced our understanding of the immunology that underpins the disease. This article reviews the biologic therapies currently available for the treatment of severe asthma.

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Introduction

Asthma is a common condition affecting an estimated 4.3% of the global population, [1] characterised by acute episodes of increased respiratory symptoms known as exacerbations. These result from expiratory airflow limitation caused by bronchial smooth muscle constriction, airways inflammation, mucus hypersecretion and airway plugging. [2]

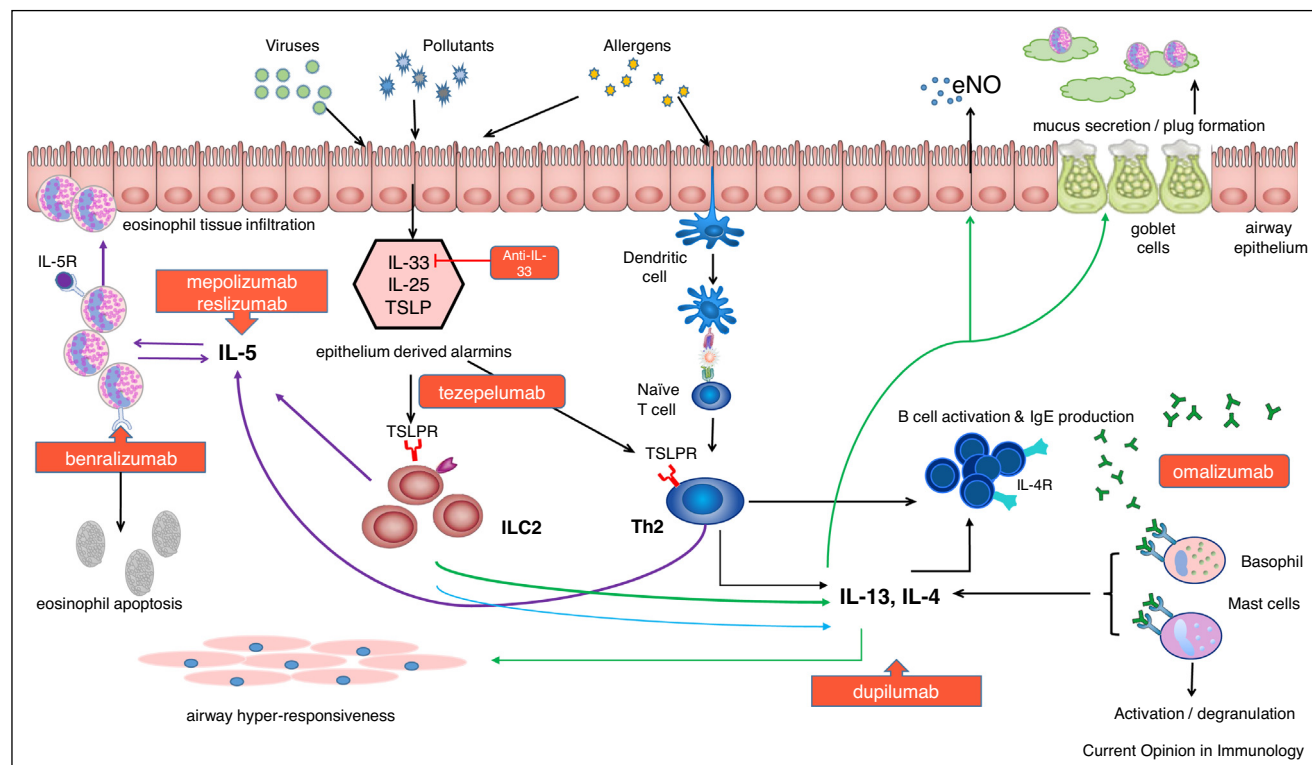
Severe asthma describes the 3–5% of all asthmatics [3] in whom symptom control cannot be achieved despite maximal therapy with inhaled corticosteroids (ICS). The most severe refractory patients have traditionally required maintenance oral corticosteroids (OCS) in an attempt to achieve control and prevent life-threatening exacerbations [4]. Whilst OCS courses remain necessary for the treatment of acute exacerbations, their recurrent or chronic use is associated with a number of complications. Treatment with systemic corticosteroids is associated with a 3.1 fold higher rate of developing an osteoporotic fracture and a 2.7 fold higher rate of pneumonia [5^{••}]. Cardiovascular and cerebrovascular events, cataracts, sleep apnoea, renal impairment, depression, anxiety, type 2 diabetes, and weight gain are also associated with systemic corticosteroid exposure [5^{••}]. Moreover, people exposed to four or more OCS courses per year have 1.3 times greater odds ratio for experiencing a new adverse event within that same year [6].

Increased awareness and prevention of steroid-induced morbidity represents an important component of the management of severe asthma and requires a multidisciplinary approach. Early attempts to reduce steroid exposure through the use of other immunosuppressive therapies including methotrexate, azathioprine and cyclosporin have been unsuccessful. [4] This lack of efficacy in part reflected a limited understanding of the dysregulated immune pathways underpinning asthma pathophysiology.

Asthmatics exhibit differential response to treatment with corticosteroids and can be placed into phenotypic clusters according to their steroid response, [7,8[•]] indicating the presence of distinct inflammatory endotypes driving pathophysiology. In particular it has become increasingly clear that the dominant inflammatory pathway underpinning severe asthma is the 'type-2' or 'T2' immune pathway. Until recently this was referred to as the T-helper 2 (Th2) pathway, but it is now appreciated that cells other than the Th2 cell are involved including type-2 innate-lymphoid cells (ILC2) [9]. These two cell types are the main, but not only, producers of the classical Th2 cytokines IL-4, IL-5 and IL-13. These cytokines and other immune mediators drive an immune response resulting in eosinophil accumulation and activation in the airway, bronchial hyper-responsiveness, mucus hypersecretion, IgE production and mast cell activation thereby driving pathophysiology in severe asthmatics (Figure 1).

Alarmins including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) released by the bronchial

Figure 1



Type 2 inflammation in the pathophysiology of asthma and the sites of action of novel biologic therapies. eNO – exhaled nitric oxide, TSLP – thymic stromal lymphopoietin, TSLP-R – thymic stromal lymphopoietin receptor, IL-25 – interleukin 25, IL-33 – interleukin 33, IL-5 interleukin 5, IL-5R – interleukin 5 receptor, IL-4 interleukin 4, IL-4R interleukin 4 receptor, IL-13 interleukin 13, Th2 – T helper 2 cell, ILC2 – type 2 innate lymphoid cells, CCL-26 – chemokine ligand 26.

epithelium play a key role in initiating the T2 response [10]. These are released in response to insult from allergens, pollutants and viruses and drive activation of the T2 cascade. Beyond Th2 and ILC2 cells, other cells implicated in the production of T2 cytokines include basophils and mast cells with some studies suggesting they are also key producers of IL-4 and IL-13 in non-exacerbating severe asthmatics [11]. Amongst T-cell populations, there is a growing appreciation that as well as CD4+ cells, a subset of CD8+ cells undergo epigenetic modification to become type 2 cytokine releasing CD8+ T-cells (Tc2) and that they play a role in asthma pathogenesis. In particular they may play an important role in steroid resistant asthma, although this is not yet fully understood [12].

As our understanding of these inflammatory cascades has grown, pharmaceutical companies have been developed targeted biologic therapies capable of reducing airways inflammation without the collateral damage associated with corticosteroids (Table 1). These monoclonal antibodies (mAbs) are directed towards various points in the T2 inflammatory cascade (Figure 1).

These therapies have transformed the lives of many people with severe asthma and have significantly reduced their steroid burden.

Therapies targeting allergic inflammation: omalizumab

Omalizumab (Xolair) was the first targeted biologic therapy developed for severe asthma and was approved by the FDA in 2003 [13]. It is a recombinant mAb that binds to IgE, preventing its ligation and subsequent cross-linking of the IgE receptor FCRI expressed on mast cells, basophils [14] and other cells including epidermal Langerhans cells [15]. Omalizumab inhibits downstream IgE signalling, resulting in a reduction in free circulating IgE of 89–99% [16]. It also decreases expression of FCRI on inflammatory cells and in so doing may help to correct the deficient anti-viral immune response observed in asthma [17]. It is dosed according to both bodyweight and circulating IgE levels and given subcutaneously every two or four weeks [16].

Guidance surrounding patient eligibility for omalizumab differs between health economies, but almost universally

Table 1
Biologic therapies for severe asthma that have reached Phase 3 clinical trials

	Target	Drug name	Mode of administration	Dosing Interval	Phase 3 studies in severe asthma	Significant results
Licenced for use in severe asthma	IgE	Omalizumab (Genentech/Novartis)	Subcutaneous injection	2 Weekly or 4 Weekly	NCT00314575 [31]	AER reduction of 25% observed in severe asthmatics compared to placebo.
		Mepolizumab (Glaxo Smithline)	Subcutaneous injection	4 weekly	DREAM [50] and MENSA [40] SIRIUS [41]	AER reduced by 59% across both identical trials in subjects with a baseline eosinophil count of ≥ 300 cells/ μ l Median reduction in OCS dose of 50% observed compared to placebo at 24 weeks.
	IL-5	Reslizumab (Teva Pharmaceuticals)	Intravenous injection	4 weekly	NCT01287039 and NCT01285323 [63] BREATH [64]	AER reductions of 50% and 59% respectively observed Significant improvement to AER lung function, symptom control and quality of life scores
		Benralizumab (AstraZeneca)	Subcutaneous injection	4 weekly for first 3 doses then 8 weekly	SIROCCO [71] and CALIMA [72] ZONDA [73**]	AER reduction in patients with baseline eosinophil count ≥ 300 cells/ μ l of 51% and 28% respectively. Note – significant placebo effect seen in CALIMA. 6 month median reduction OCS dose 50% versus placebo
	IL-4 receptor	Dupilumab (Sanofi / Regeneron)	Subcutaneous injection	2 weekly	LIBERTY ASTHMA QUEST [98*] LIBERTY ASTHMA VENTURE [86**] STRATOS 1 and STRATOS 2 [96*] TROPOS [98*]	AER and lung function improved in treatment arm. Most pronounced when eosinophil count ≥ 300 cells/ μ l, (AER reduction 66–67%) Effective OCS sparing agent: Median OCS dose was reduced by 50% versus placebo No improvement in AER compared to placebo No significant steroid sparing effect compared to placebo
Phase 3 studies completed but further development ceased	IL-13	Tralokinumab (MedImmune /AstraZeneca)	NA	NA	LAVOLTA I and LAVOLTA II [97] NAVIGATOR (NCT03347279) and DIRECTION (NCT03927157) [105]	No improvement in AER compared to placebo Exacerbation reduction studies
		Lebrokizumab (Genentech)	NA	NA	SOURCE NCT03406078 [105]	No improvement in AER compared to placebo OCS dose reduction study
Currently in Phase 3	TSLP	Tezepelumab (Amgen/ AstraZeneca)	Subcutaneous injection	NA		

AER – annualised exacerbation rate, OCS – oral corticosteroids, IL- interleukin, TSLP – thymic stromal lymphopoietin.

includes the presence of an atopic phenotype, evidence of sensitisation to perennial allergen, and history of poorly-controlled asthma and/or frequent exacerbations despite high-dose ICS. A Cochrane review published in 2014 [18] identified 19 studies that considered the efficacy of omalizumab as an adjunct to treatment with corticosteroids. However only the study by Hanania *et al.* [19] restricted inclusion to severe asthmatics. Even in that trial [19] the annualised exacerbation rate (AER) per patient in the placebo arm was only 0.88 per year, suggesting that most subjects did not have severe asthma. The AER in the omalizumab arm was 0.66, reflecting a 25% reduction in exacerbations. Efficacy differs according to baseline background treatment. Those subjects on high-dose ICS/LABA without additional controllers such as a LTRA experienced a 34% reduction in exacerbations versus placebo; those on an additional controller were shown

to have a 28% reduction in exacerbations; whereas the most severe subjects on maintenance OCS failed to derive any benefit in terms of exacerbation reduction from omalizumab [19].

Real-world prospective studies have confirmed the ability of omalizumab to significantly reduce AER. The APEX II study included 258 adult patients with poorly-controlled atopic asthma and recurrent exacerbations. The authors reported a reduction in AER from 1.66 to 0.69, alongside significant improvements in FEV1, symptom and quality of life scores. A positive socio-economic impact with reduced mean sick days following initiation, fewer emergency department visits and a significant reduction in the number of hospitalisations was also observed. [20] However the ability of omalizumab to permit a meaningful reduction in maintenance OCS dose was less impressive:

a reduction of the mean daily dose of prednisolone from 15.4 mg/day to 13.0 mg/day was statistically significant, but of questionable clinical importance. This is in line with the results from the Hanania study [19] and together suggests that omalizumab appears to be less efficacious in patients dependent on maintenance OCS. No large-scale phase 3 studies of the utility of omalizumab in patients requiring maintenance OCS have been performed. The largest real-world efficacy data for omalizumab comes from a recently published Japanese study [21] which included 1 year data on 3620 patients. This reported that 48% of the patients were exacerbation-free after commencing omalizumab, however it also highlighted that 42% of the patients continued to experience ≥ 2 exacerbations [21].

Predictors of response to omalizumab

Several biomarkers have been evaluated as potential predictors of responsiveness of omalizumab therapy. These include increased fraction of exhaled nitric oxide (FeNO), blood eosinophil count, periostin (commercially unavailable), total IgE and antigen-specific IgE [22,23]. Eosinophil counts ≥ 300 cells/mL are associated with higher disease activity and better response to omalizumab [24,25]. Moreover, subjects treated with omalizumab therapy with higher peripheral blood eosinophil counts are more likely to suffer asthma exacerbations if omalizumab is discontinued [26].

FeNO is a well-validated biomarker of airways inflammation in asthma, which can be easily and noninvasively measured in the clinic [27]. An elevated FeNO at baseline appears to be associated with a greater response to omalizumab in terms of exacerbation reduction [22,28]. Similarly, an increase in FeNO after discontinuation of long-term omalizumab predicts subsequent exacerbations [26].

Interestingly total IgE has not been shown to be a reliable predictor of response to omalizumab treatment highlighting that our understanding of the mechanism of action of this therapy is far from complete [23].

Therapies targeting Interleukin-5

Interleukin-5 (IL-5) is the major cytokine associated with the eosinophil, a granulocyte believed to be central to parasite immunity. IL-5 also has a role in B-cell antibody production and isotype switching. The major source of IL-5 in the pathogenesis of asthma are the Th-2 and ILC-2 cells, however it is both produced by, and is a driver of growth and differentiation of, eosinophils [29,30]. The role of the eosinophil in asthma has been recognised for over 60 years [31–33]. Treatment algorithms guided by measurement of sputum eosinophilia rather than symptoms have been shown to result in improved health outcomes [34], whilst a subsequent study of 24 117 participants found a clear relationship between the level of

blood eosinophils and both asthma control and exacerbation risk [35]. Reducing eosinophil numbers and activation, as occurs with corticosteroid use, is therefore highly desirable in the management of severe asthma. Targeting IL-5 represents one approach to achieving this without exposing patients to high doses of steroid.

Mepolizumab

Mepolizumab is a fully-humanised, serum-neutralising antibody which binds with high affinity to IL-5, preventing IL-5 binding to the α -unit of the IL-5 receptor subchain, thereby inhibiting downstream signalling cascades [36,37]. In early mechanistic studies, mepolizumab was shown to almost completely deplete blood eosinophils and was additionally shown to reduce eosinophil levels in bone marrow by 52% and airway by 55% [38–50].

Three clinical trials have established the utility of mepolizumab in severe asthma. The primary efficacy outcome measure of the phase 2b DREAM [50] and phase 3 MENSA [40] trials was the ability to reduce AER in patients with evidence of uncontrolled eosinophilic asthma. In both studies, all doses used showed statistically significant reductions in AER leading to the decision to license the 100 mg subcutaneous dose in severe eosinophilic asthma. At this dose, a 53% reduction in AER was observed compared to placebo [40]. Combined analysis of MENSA and DREAM showed a 59% reduction in AER in subjects with a baseline eosinophil count of ≥ 300 cells/ μ L [51]. Of note, the effect on lung function, quality of life measures and symptom burden scores was less pronounced suggesting that these outcome measures are less IL-5 dependent [40,50,51].

The phase 3 SIRIUS study [41] recruited subjects with OCS-dependent eosinophilic asthma and assessed the ability of mepolizumab to act as a steroid-sparing agent. At 24 weeks, a median reduction in OCS dose of 50% was observed compared to placebo, with 54% of subjects able to reduce their maintenance OCS dose by $\geq 50\%$ (versus 33% treated with placebo). 14% were able to completely stop their maintenance OCS (versus 8% in placebo arm), whilst 36% were either unable to reduce their OCS at all or withdrew from the study. Despite this reduction in OCS treatment, a 32% reduction in AER was also observed in subjects treated with mepolizumab (AER 1.44 versus 2.12 with placebo) [41]. COSMOS, an extension study which recruited subjects from both SIRIUS and MENSA, further confirmed the safety profile and clinical efficacy over an additional year of study [52]. More recently the long-term extension COLUMBA study which enrolled subjects from DREAM reported continued clinical efficacy and safety up to 4.5 years [53].

Post-hoc analysis of phase 3 trials have highlighted that the most important predictors of response to mepolizumab are previous exacerbation rates and baseline blood

eosinophil counts [40,50,51,54,55]. Specifically, the higher the eosinophil count and more frequent the baseline exacerbations, the greater the clinical efficacy. In contrast, efficacy was found to be independent of baseline IgE and atopic status [56,57]. Prior treatment with omalizumab does not predict efficacy of mepolizumab [58–60].

Published real world experience of mepolizumab confirms the results of the controlled studies with a 52% reduction in AER reported after one year of treatment. Additional impressive reductions in mOCS requirements were reported with over 70% of patients with SEA able to reduce their mOCS dose by at least 50% [106]. Interestingly it has been shown that a decline in adherence to ICS was associated with less marked improvements in exacerbation rate in this cohort highlighting the need to assess adherence to background therapy in apparent mepolizumab non-responders [107].

Reslizumab

Reslizumab is a recombinant humanised mAb (IgG4κ), given intravenously, which binds with high-affinity to IL-5 [61]. With a similar mechanism of action to mepolizumab, reslizumab lowers circulating blood eosinophil levels [62]. Two phase 3 controlled trials of reslizumab showed significant reductions in AER with statistically significant risk ratios of 0.50 and 0.41 respectively [63]. In addition, the BREATH trial showed reslizumab improved other outcome measures including lung function, symptom control and quality of life scores [64]. In post-hoc analyses of BREATH, the greatest response to reslizumab was observed in patients with a late-onset asthma phenotype, [65] and in those with more severe disease [66].

In contrast to the phase 3 program for mepolizumab and benralizumab, an OCS reduction study has not been performed for intravenous reslizumab, resulting in an evidence gap for this severe refractory cohort. Additionally, despite excellent clinical efficacy, the intravenous formulation makes delivery of care more resource intensive when compared to mepolizumab or benralizumab. Two phase 3 studies conducted with subcutaneous reslizumab have now been reported with disappointing results showing at the dose used there was no significant improvement in AER or OCS reduction [67**].

Benralizumab

Benralizumab acts as a competitive inhibitor to IL-5 by binding with high-affinity to the α-subunit of IL-5 receptor (IL5α) (CD125) expressed on eosinophils, eosinophilic precursors and basophils [68]. It therefore has a different mechanism of action to the serum neutralising IL-5 mAbs mepolizumab and reslizumab. Benralizumab induces a process known as enhanced antibody mediated cytotoxicity leading to the apoptosis by natural killer cells

of cells expressing IL5α [29,68]. Through this mechanism, benralizumab leads to the near-complete depletion of blood eosinophils within 24 hours of administration and a more marked depletion of airway eosinophils than is seen with the licensed dose of mepolizumab [69,70]. Although there have been some concerns around the theoretical risks associated with eosinophil depletion, particularly in relation to host defence, these concerns have thus far been proven unwarranted with no safety signals identified across multiple studies. Indeed it increasingly appears that there is sufficient redundancy within the immune system for eosinophils to no longer be required in health [108].

Three phase 3 trials have assessed the clinical efficacy of benralizumab, SIROCCO [71], CALIMA [72] and ZONDA [73**]. SIROCCO and CALIMA both demonstrated that benralizumab could effectively reduce exacerbations in patients with severe uncontrolled asthma and a baseline eosinophil count ≥ 300 cells/ μ l. SIROCCO reported a 51% reduction in exacerbations, with a more modest reduction of 28% observed in CALIMA in the context of a very marked placebo response. Both studies also showed statistically significant improvements in lung function, asthma control and quality of life measures [71,72].

ZONDA assessed benralizumab's ability to reduce maintenance OCS requirements. At 6 months, a median reduction in dose of 50% versus placebo was seen which matched the results in the equivalent mepolizumab OCS reduction study SIRIUS [41,73**]. In Zonda, benralizumab allowed 52% of eligible subjects to completely stop maintenance OCS compared to 14% with mepolizumab in SIRIUS; despite this the exacerbation rate was reduced by 70% with benralizumab, compared to 32% with mepolizumab.

In keeping with results from mepolizumab analyses, a sub-group analysis of SIROCCO and CALIMA confirmed increasing efficacy in patients with higher blood eosinophil counts and a greater baseline exacerbation rate [74*]. Pooled analysis of these studies found that the best predictors of response to benralizumab are nasal polyposis, pre-bronchodilator FVC < 65% predicted, ≥ 3 exacerbations in the preceding year and adult-onset asthma [75,109,110,111].

In a large real-world of 130 patients, benralizumab led to a median reduction in mOCS dose of 100% by 1 year, whilst AER reduced by 72.8% [105]. Indeed such an effective steroid-sparing option has created new clinical challenges for physicians with regards to adrenal insufficiency of previously prednisolone dependent patients [111]. An analysis of 'super-responders' to benralizumab highlighted higher pre-treatment eosinophil count, adult-onset disease and nasal polyposis as all being

associated with a particularly marked response to treatment, very much supporting the post-hoc analyses of the phase 3 results. Interestingly, clinical efficacy has been shown to be independent of baseline IgE highlighting the central role of the eosinophil in the pathogenesis of SEA [110].

Therapies targeting interleukin-4 and interleukin-13

IL-4 and IL-13 are two functionally overlapping, key regulators and drivers of T2 inflammation. They are produced by basophils, mast cells, ILC-2 cells, TH-2 cells, and the T2 polarised CD8⁺ Tc2 cells [10[•], 11, 12[•], 76, 77]. Single nucleotide polymorphisms at a locus in which the *IL4* and *IL13* genes are contained are associated with asthma [78[•]] whilst epigenetic modification of these genes are also associated with asthma [79]. IL-4 is thought to play a greater regulatory role by expanding the Th-2 cell population and driving IgE production by B cells as well as promoting eosinophil exotaxis from the airway, whilst IL-13 has a key role in airway hyper-responsiveness, mucus hypersecretion and airway remodelling in asthma [10[•], 77]. In addition, as IL-13 and the IL-13 dependent chemokine CCL-26 / Eotaxin-3 is important in the migration of eosinophils from the blood to tissue, an approach that blocks IL-13 could also reduce eosinophil numbers in the lung [80, 81]. This makes IL-4 and IL-13 blockade an appealing strategy in modifying disease mediated by type 2 inflammation.

IL-4 and IL-13 blockade: dupilumab

Dupilumab is a fully humanised IgG4 monoclonal antibody directed against the α -subunit of the IL-4 receptor (IL-4R). IL-4 and IL-13 both act as ligands to IL-4R, therefore dupilumab is able to suppress IL-4 and IL-13 mediated pathways [82]. The reductions in total IgE and FeNO levels observed in clinical trials confirm its mechanism of action further [83, 84^{••}]. Dupilumab is also licenced for use in moderate to severe atopic dermatitis (AD) and may become the first-line option in patients with both severe asthma and severe AD [85].

The phase 3 LIBERTY ASTHMA QUEST study showed that dupilumab is able to reduce AER and improve lung function [84^{••}, 104]. This effect was more pronounced in subjects with a peripheral eosinophil count ≥ 300 cells/ μ l, in whom a reduction in AER of around 67% was observed, approximately double the reduction seen in subjects with an eosinophil count between 150 and 300 cells/ μ l, whilst it was ineffective in those with an eosinophil count < 150 cells/ μ l [84^{••}, 104]. A similar pattern of response was observed for FeNO, with the greatest efficacy seen in subjects with a FeNO ≥ 50 ppb.

The LIBERTY ASTHMA VENTURE trial [86^{••}] showed dupilumab to be an effective steroid-sparing agent in patients requiring maintenance OCS. Median

OCS dose was reduced by 50% versus placebo, whilst 69% of participants reduced their dose to less than 5 mg a day, compared to 33% in the placebo group and 48% stopped completely (versus 25% in placebo) [86^{••}].

Dupilumab was approved for the treatment of asthma by the FDA in 2018 and the EMA in 2019 [87]. The two-weekly dosing schedule may represent a potential disadvantage for some patients. In addition, the phase 3 studies highlighted a high rate of injection site reactions (18.4% in QUEST) compared to the other biologic treatments licensed for asthma [84^{••}].

IL-13 blockade: tralokinumab and lebrikizumab

Attempts to target IL-13 alone have been less successful. Tralokinumab and lebrikizumab are both mAbs targeting IL-13 [88–91]. Although Phase 2 studies were encouraging [92–95], results from Phase 3 studies, have disappointed [96[•], 97, 98[•]]. This is probably a consequence of the functional overlap of IL-4 and IL-13 signalling that exists thanks to the presence of a shared receptor which elicits downstream signalling of both cytokines. Another unsuccessful mAb has been fevipiprant, which targets prostaglandin D₂, an upstream mediator of T2 inflammation. Phase 3 trials showed no significant reduction in AER and development has now ceased [112, 113].

Therapies targeting thymic stromal lymphopoietin: tezepelumab

Tezepelumab is a human monoclonal antibody that binds to TSLP, an epithelium-derived alarmin that is heavily implicated in the pathogenesis of asthma [99–101]. It binds to a region which prevents TSLP binding to its receptor [102] thus inhibiting downstream signalling. Phase-3 studies are ongoing at the time of writing but early studies have been encouraging. In a phase 2 dosing study of 584 adult patients (GINA stage 3 and 4) [103] AER decreased in the treatment groups by 61–71%. Importantly this result was preserved in patients with eosinophil counts of < 250 cells/ μ l, was independent of IgE level and was maintained at 52 weeks. It was also shown to improve lung function and reduce FeNO, serum IgE and peripheral eosinophil count. Its ability to affect eosinophil count, FeNO and IgE supports the role of TSLP as a key upstream mediator of T2 inflammation.

Conclusions

Severe asthma accounts for a small proportion of total asthma cases, but accounts for disproportionate use of healthcare resource. Historically, physicians have relied upon high dose ICS and OCS but this has come at a substantial cost to patients as a consequence of steroid-related morbidity. Elucidation of the T2 inflammatory cascade and the development of T2-modulating mAbs has opened new, life-changing treatment options for the severe asthmatic patient. Early results with these agents are very promising and with additional therapies in

development there is further cause for optimism. Nonetheless the high cost of these therapies means patient selection is key. Specifically, physicians need to clearly identify those patients in whom T2 inflammation is resistant to ICS and is driving immunopathology in order to achieve optimal responses. Indeed, as these new biologic treatments have been developed and post-hoc analyses have been conducted, they have helped further elucidate the roles of different elements of the T2 pathway and have added to our understanding that even T2-high asthma is highly heterogenous with multiple different sub-endotypes. As we continue to learn why individual patients respond differentially to individual biologics, we will move further towards a biomarker directed, individualised approach to their selection.

Conflict of interest statement

APH is undertaking a PhD which will receive funding from AstraZeneca. BDK has taken part in advisory boards for GSK and AstraZeneca. He has received speaker fees from GSK, AstraZeneca, Chiesi, and Novartis. He has received educational bursaries from Boehringer Ingelheim, Chiesi, and Napp. DJJ reports advisory board, speaker fees and conference travel support from AstraZeneca, Sanofi, Boehringer Ingelheim, Teva, GlaxoSmithKline and Novartis.

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- of outstanding interest

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